Current Clinical Urology
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Jeffrey S. Palmer, MD
Editor

Pediatric Urology

A General Urologist's Guide

Humana Press

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CURRENT CLINICAL UROLOGY

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A General Urologist's Guide

Edited by

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Pediatric and Adolescent Urology Institute,
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Cleveland Clinic Lerner College of Medicine of Case Western Reserve University,
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This book is dedicated to my parents, whose love, support, dedication, and sacrifices have enabled their children to be the best that they could become. I thank them both from the bottom of my heart.

Preface

Pediatric urology covers a wide range of medical conditions from those managed medically (e.g., voiding dysfunction) to those managed surgically (e.g., bladder exstrophy). Although some conditions are similar in both children and adults, such as hematuria and hydroceles, their etiology and management may be different. This has led to the commonly accepted principle that children with urologic conditions should not be treated as small adults. Unlike adults, the ratio of congenital to acquired conditions in children with urologic conditions is much higher. Congenital and acquired conditions in children may require observation (e.g., hydronephrosis and renal trauma, respectively), reconstruction (e.g., urethroplasty for hypospadias and buccal mucosal urethroplasty for failed urethroplasty), or excision (e.g., heminephrectomy associated with an ectopic ureter and orchiectomy for testicular torsion).

Due to the relatively few fellowship-trained pediatric urologists in the United States, a vast number of children are evaluated and treated for urologic conditions by urologists practicing general urology. *Pediatric Urology: A General Urologist's Guide* is written specifically for general urologists as a concise and comprehensive reference of the more common pediatric urologic conditions. Other health practitioners (i.e., pediatricians, family practitioners, residents, medical students, and midlevel providers) will also find this book as a key reference.

Well-respected pediatric urologists have been carefully chosen to author the chapters due to their expertise. This will assist the healthcare provider to rapidly review the essential aspects of the physical examination, evaluation, diagnostic testing, and management while the patient is still in the office. The chapters are also arranged into four sections to allow for easier access to the information: office urology, genitalia, urinary tract, and miscellaneous topics. Furthermore, the first chapter is dedicated to facts and figures that serve to allow easy access to this information. Upon completion of this text, it is my sincere hope that the reader will have the essential information to assist them in the care of children.

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I Office Urology

1 Pediatric Urology Facts and Figures

David M. Kitchens
and C. D. Anthony Herndon

Table 1.1
Mean blood pressure norms for boys and girls

Age	*Boys (mmHg)*	*Girls (mmHg)*
1 year		
Systolic blood pressure (SBP)	98–101	98–102
Diastolic blood pressure (DBP)	52–54	54–58
2 years		
Systolic blood pressure (SBP)	100–104	101–106
Diastolic blood pressure (DBP)	55–58	58–62
3 years		
SBP	101–105	102–107
DBP	58–61	60–65
4 years		
SBP	102–107	103–108
DBP	60–64	62–67
5 years		
SBP	103–108	104–110
DBP	63–67	64–70
6 years		
SBP	105–110	105–111
DBP	66–69	67–71

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Table 1.1
(continued)

Age	*Boys (mmHg)*	*Girls (mmHg)*
7 years		
SBP	106–111	106–112
DBP	68–71	68–72
8 years		
SBP	107–112	107–113
DBP	69–73	69–73
9 years		
SBP	107–114	108–114
DBP	70–74	71–73
10 years		
SBP	108–116	109–116
DBP	72–76	72–73
11 years		
SBP	110–118	111–120
DBP	74–76	74–75
12 years		
SBP	113–122	114–122
DBP	75–76	75–76
13 years		
SBP	115–126	116–123
DBP	74–77	75–76
14 years		
SBP	119–129	118–123
DBP	74–80	76–77
15 years		
SBP	123–130	118–124
DBP	75–81	76–78
16 years		
SBP	126–132	119–124
DBP	77–82	76–78
17 years		
SBP	128–134	120–125
DBP	78–83	76–78

Adapted from Rosner, B et al. *Determination of Blood Pressure Percentiles in Normal-Weight Children: Some Methodological Issues*. American Journal of Epidemiology. 2008; 167(6):663.

Table 1.2
Mean fetal renal length

Weeks gestational age	*Longitudinal mean (cm)*	*Transverse mean (cm)*
16–20	1.7–2.1	1.0–1.4
21–24	2.1–2.8	1.5–1.7
25–28	2.9–3.3	1.6–1.9
29–32	3.5–3.7	2.0–2.1
33–36	3.7–4.1	2.2–2.5
37–40	4.2–4.3	2.4–2.6

Adapted from Shin, JS et al. *Nomogram of Fetal Renal Growth Expressed in Length and Parenchymal Area Derived From Ultrasound Images*. The Journal of Urology. 2007; 178(5):2153.

Table 1.3
International grading system for VU

Grade I	Ureter only
Grade II	Ureter and renal pelvic and calices without dilation
Grade III	Moderate tortuosity and dilation of ureter and renal pelvis, blunting of calices
Grade IV	Moderate tortuosity and dilation of ureter and renal pelvis, obliteration of sharp angles of fornices but papillary impression in majority of calices
Grade V	Severe tortuosity and dilation of ureter, pelvis and calices, papillary impression are not present
International system of radiographic grading of vesicoureteric reflux. International Reflux Study in Children	

Reprinted from Lebowitz RL. *Literature in Pediatric Urology*. Pediatric Radiology. 1985; 15(2):105–9.

Table 1.4
Bladder capacity

Age + 2= oz × 30 = cc	
<2 yr	2× age (years) + 2=oz ×30 =cc
>2 yr	Age (years)/2 + 6= oz ×30=cc

Reprinted from Kaefer M. et al. *Estimating Normal Bladder Capacity in Children*. The Journal of Urology. 1997; 158:(6) with permission from Elsevier

Table 1.5
Society for fetal urology hydronephrosis classification

Society for fetal urology hydronephrosis classification	
0	No renal pelvis splitting
1	Renal pelvis dilation/splitting only (Fig. 1.1)
2	Renal pelvis dilation/some calyceal dilation (Fig. 1.2)
3	Renal pelvis dialation, all calyceal dilation but no parenchymal thinning (Fig. 1.3)
4	Renal pelvis dialation, all calyceal dialation may be convex, parenchymal thinning is present (Fig. 1.4)
Society for fetal urology ureteral dilation classification	
1	< 7 mm
2	7–10 mm
3	>10 mm

Reprinted from Maizels M. et al. *Grading Nephroureteral Dilatation Detected in the First Year of Life: Correlation with Obstruction*. The Journal of Urology. 1992; 148: 609–614 with permission from Elsevier

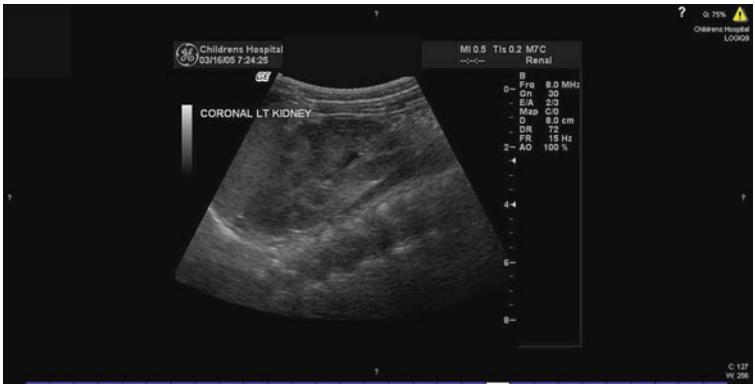


Fig. 1.1 SFU Grade 1 hydronephrosis

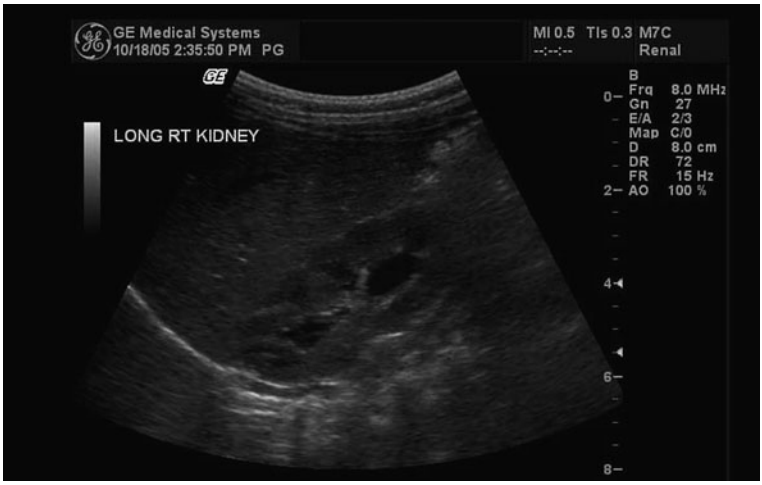


Fig. 1.2 SFU Grade 2 hydronephrosis

Fig. 1.3 SFU Grade 3 hydronephrosis

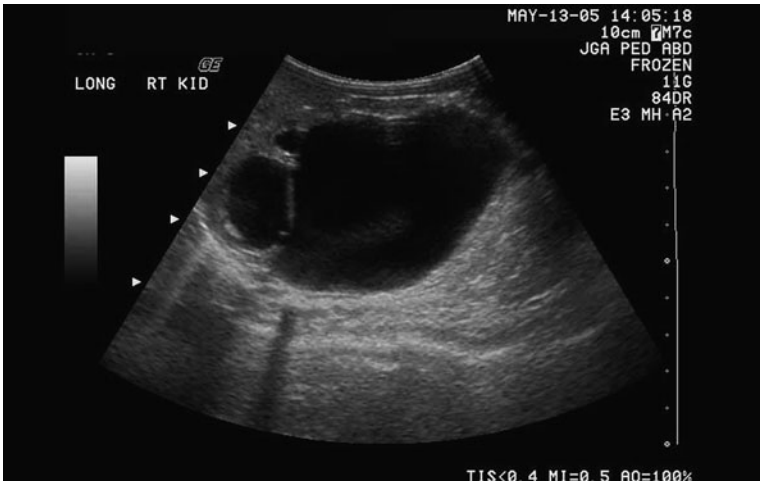


Fig. 1.4 SFU Grade 4 hydronephrosis

Table 1.6
Tanner staging

	Male	*Female*
Stage I	Pre-adolescent; no pubic hair	Pre-adolescent; no pubic hair
Stage II	Sparse long, slightly pigmented downy hair, straight or slightly curly, appearing mostly at base of penis	Sparse long, slightly pigmented downy hair, straight or slightly curly, appearing most along labia
Stage III	More dark, coarse and curled. Spreads over pubis	More dark, coarse and curled. Spreads over pubis
Stage IV	Hair is adult type but smaller area. No hair on inner thighs	Hair is adult type but smaller area. No hair on inner thighs
Stage V	Adult quantity and quality, inverse triangle, inner thighs but not above linea alba	Adult quantity and quality, inverse triangle, inner thighs but not above linea alba
Stage VI	Wide spread pubic hair above pubis (mid-twenties)	
	Male genitalia	*Female breast*
Stage I	Pre-adolescent; testes, scrotum and penis are same size and proportion as childhood	Pre-adolescent; papilla elevation only
Stage II	Scrotum and testes enlarged with change in scrotal skin (some reddening)	Breast bud stage; elevation of breast and papilla as a mound, enlargement of areola
Stage III	Growth of penis, mostly length but some breadth. Further growth of testes and scrotum.	Enlargement of breast and areola, with no separation of contours
Stage IV	Penis further enlarged in length and breadth with development of glans. Testes and scrotum further enlarged. Darkening of scrotal skin	Projection of areoa and papilla to form a secondary mound above the level of the breast
Stage V	Genitals adult size and shape	Mature stage; projection of papilla only, recession of areoa to the general contour of the breast

Adapted from Marshall WA, Tanner, JM. *Variations in Pattern of Pubertal Changes in Boys*. Archives of Disease in Childhood. 1970; 45:13–14.

Adapted from Marshall WA, Tanner, JM. *Variations in Pattern of Pubertal Changes in Girls*. Archives of Disease in Childhood. 1969; 44:291–292.

Table 1.7
Treatment options for constipation

Fiber supplements	
Metamucil (wafers, capsule, powder)	
Benefiber (powder, chewable tablet, candy drops)	
FiberCon caplet	
Citrucel caplet	
FiberChoice Chewable tablet	
Colonic motility agents	
Polyethylene Glycol 3350(MiraLax)	> 5 yrs 17 g, < 5 years 8.5 g
Lactulose	15 cc po qd
Mineral Oil	1–2 tbls prn
Colace	> 12 yrs 50–200 mg qd, 6–12 yrs 40–120 mg/qd, 3–6 yrs 2 cc Liq tid
Glycerin suppository	2–5 yrs 1 g, > 6 yrs 2–3 g
Senokot Children's	6–11 yrs 5–7.5 cc qhs, 2–5 yrs 2.5–3.75 cc qhs

Reprinted from Herndon CD, Joseph DB. *Urinary Incontinence*. Pediatric Clinics. 2006; 53:363–377 with permission from Elsevier

Table 1.8
Oral treatment options for dysfunctional voiding

Anticholinergics	*Dose*	*Max*
Ditropan (Oxybutynin Chloride)	0.2 mg/kg/dose	0.6 mg/kg/day
Ditropan XL (Oxybutynin Chloride)	5 mg qd	15 mg qd
Levsin (Hyoscyamine sulfate)	0.03 mg/kg bid	0.1 mg/kg bid
Pro-Banthine (Methantheline bromide)	0.5 mg/kg bid	0.5 mg/kg qid
Detrol (Tolterodine tartrate)	0.02 mg/kg bid	2 mg bid
Detrol LA (Tolterodine tartrate)	2 mg qd	4 mg qd
Alpha-1 Adrenergic Blockers		
Flomax (Tamsulosin)	0.4 mg qhs	0.4 mg qhs
Uroaxtral (Afluzosin)	10 mg qhs	10 mg qhs
Cardura (Doxazosin)	0.5 mg qhs	1–2 mg qhs
Hytrin (Terazosin)	1 mg qhs	2–4 mg qhs

Reprinted from Herndon CD, Joseph DB. *Urinary Incontinence*. Pediatric Clinics. 2006; 53:363–377 with permission from Elsevier

Table 1.9
Normal serum creatinine levels based on age

Age	*Creatinine, Blood*
0–2 years	0.2–0.6 mg/dl
8 years	0.3–0.7 mg/dl
11–13 years	0.4–0.8 mg/dl
14–17 years	0.4–0.9 mg/dl
> 16 years	0.7–1.5 mg/dl

1997 Children's Hospital of Alabama Handbook

Table 1.10
Vesicoureteral reflux resoltion rates

VUR resolution	*1 year*	*3 years*	*5 years*
Grade I	39%	78%	92%
Grade II	28%	63%	81%
Grade III unilateral (2–5 years)	13%	35%	51%
Grade III bilateral (0–2 years)			
Grade III bilateral (2–5 years)	7%	20%	30%
Grade IV unilateral	16%	41%	58%
Grade IV bilateral	4.00%	8.00%	10%

Adapted from AUA Pediatric Vesicoureteral Reflux Guidelines Panel. http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/patient-guides/pedreflux.pdf Accessed May 26, 2010.

Table 1.11
Mean renal length: sonography

Renal length	*cm*
0–6 months	4.5–6.2
6–10 months	6.2
1.5–3.5 years	6.6–7.4
3.5–5.5 years	7.4–8.0
5.5–7.5 years	8.1–8.3
7.5–9.5 years	8.3–9.2
9.5–11.5 years	9.2–9.6
11.5–13.5 years	9.6–9.8
13.5–16.5 years	9.8–10.0
16.5–18.5	10.0–10.8

Adapted from Rosenbaum DM, Korngold E, Teele RL. Sonographic Assessment of Renal Length in Normal Children. http://www.ajronline.org/cgi/reprint/142/3/467.pdf Accessed May 26, 2010.

Table 1.12
Double JJ Ureteral stent size

Age (years) + 10 = length in cm

Adapted from Palmer JS, Palmer LS. *Determining the Proper Stent Length to Use in Children: Age Plus 10*. The Journal of Urology. 2007; 178:1566–1569.

Table 1.13
Commonly prescribed antibiotics

Oral antibiotics	*Dose*	*Max*
Macrodantin (Nitrofurantoin)	1.5 mg/kg/dose qid	400 mg qd
Bactrim, Septra (Sulfamethoxazole/Trimethroprim)	5 mg/kg/dose bid (Trimethoprim)	1600 mg qd (Trimethoprim)
Keflex (Cephalexin)	10 mg/kg/dose qid	4000 mg qd
Cipro (Ciprofloxacin)	10 mg/kg/dose bid	1500 mg qd
Intravenous antibiotics	*Dose*	*Max*
Ampicillin	50 mg/kg/dose qid	12000 mg qd
Gentamicin	2 mg/kg/dose bid	based on serum levels
Fortaz (Ceftazidime)	50 mg/kg/dose tid	6000 mg qd

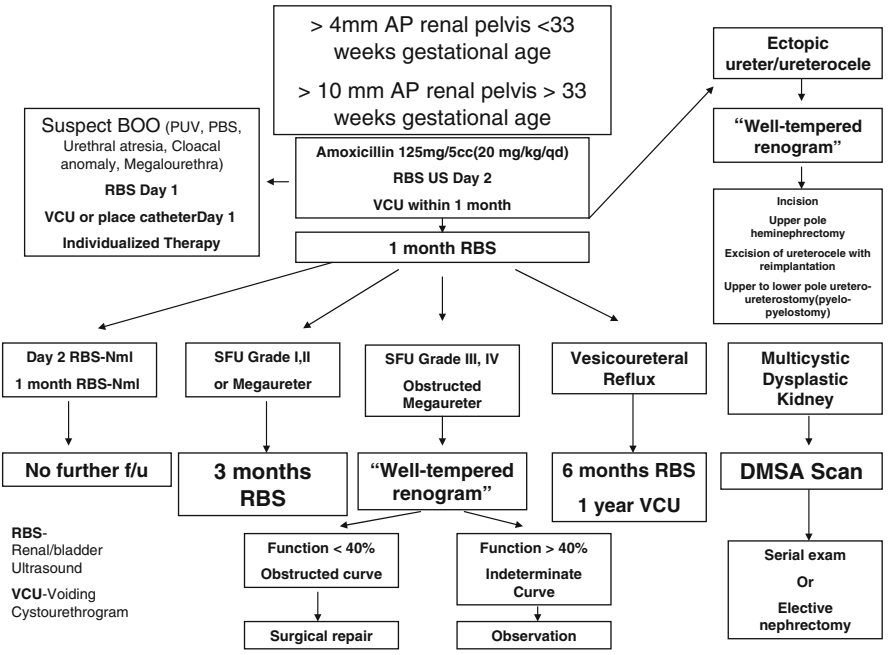
Adapted from Lexi-Comp ONLINE. http://online.lexi.com/crlonline

Table 1.14
Normal stretched penile length by age

Age	*Length (cm)*
Birth	>2
2 years	>2.5
4–12 years	>4
14 years	>5
16 years	>6
20 years	>8

Adapted from Aaronson IA. *Micropenis: Medical and Surgical Implications*. The Journal of Urology. 1994; 152:4–14.

Table 1.15
Prenatal hydronephrosis: postnatal evaluation



Reprinted from Kitchens DM, Herndon CD. Curr Urol Rep. 2009; 10 (2): 126–133. Review

2 Radiographic Imaging

Lane S. Palmer

Abstract The evaluation of children with urologic complaints or possible congenital anomalies cannot go forward without proper imaging. The mainstay of this imaging includes ultrasonography, voiding cystourethrography (VCUG), and nuclear scintigraphy. Each modality has its distinct indications and complements each other with the goal of defining the normal or anomalous genitourinary tract. Ultrasound allows for excellent screening of the kidneys and bladder in children presenting with various complaints, primarily urinary tract infections, or for various syndromes that affect the urinary tract; moreover, it serves to confirm prenatal ultrasound findings. VCUG, while invasive, is the gold standard for determining the presence of vesicoureteral reflux and is helpful in documenting other anomalies such as posterior urethral valves, ureteroceles, and diverticulae. Nuclear studies provide helpful information regarding differential function as well as drainage (MAG3) but can also help in determining parenchymal integrity (DMSA); i.e., scarring versus pyelonephritis. Finally, ultrasound and nuclear studies are vital adjunctive studies to help define scrotal pathology, both acute and chronic.

Keywords Radiology · Pediatric urology · Ultrasound · Children · Congenital

INTRODUCTION

The mainstay of imaging the genitourinary tract of children remains the ultrasound, voiding cystourethrography (VCUG), and diuretic renography. Using these three modalities, the nature of the genitourinary tract remains ambiguous in very few children. In the few cases where there remains a question regarding the status of the urinary tract, improvements in CT and MRI now offer us superior adjunctive studies and may be the definitive study. Spiral CT offers considerable benefits for investigating stone disease, trauma, and tumor staging. MRI continues to mature as an imaging study for complex anomalies but also may have a role in evaluating obstruction and infection (*1*, *2*). In this chapter, we will not go into significant depth into

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the anomalies of the genitor-urinary tract as they will be covered in other chapters but we will rather review the imaging findings associated with these anomalies.

IMAGING MODALITIES

Ultrasound: Ultrasound is the most commonly performed study of the urinary tract. It is a quick study to perform, provides very good anatomic detail, and is non-invasive without the use of ionizing radiation. There are several indications for performing ultrasound in children (Tables 2.1 and 2.2), including detecting anatomic abnormalities that may explain the etiology of urinary tract infections (*3*), and the primary study of the acute scrotum in many institutions (*4*). It is routinely performed prenatally as a screening tool for congenital anomalies.

The evaluation of the urinary tract in children should routinely include the kidneys (Fig. 2.1) and the bladder. The images of the kidneys should be

Table 2.1
Indications for performing renal and bladder ultrasound in children

Urinary tract infection – febrile
Urinary tract infection – recurrent non-febrile
Voiding dysfunction
Prenatal renal abnormality
Renal colic
Palpable abdominal mass
Single umbilical artery
Hypertension
Hematuria
Proteinuria
Family history polycystic kidney disease
Hemihypertrophy
Azotemia
Urinary retention
Syndrome associated with renal involvement (e.g., Tuberous sclerosis, CHARGE, VACTERL, WAGR, Beckwith-Wiedeman, etc.)
Surveillance of
Vesicoureteral reflux
Nephrolithiasis
Hydronephrosis
Cystic renal disease
Neurogenic bladder dysfunction (e.g., myelodysplasia)
Obstructive uropathy (e.g., posterior urethral valves)

Table 2.2
Indications for performing scrotal ultrasound in children

Palpable intrascrotal mass
Acute scrotal pain
Acute scrotal swelling
Chronic scrotal pain
Chronic scrotal swelling
Varicocele
Testicular asymmetry

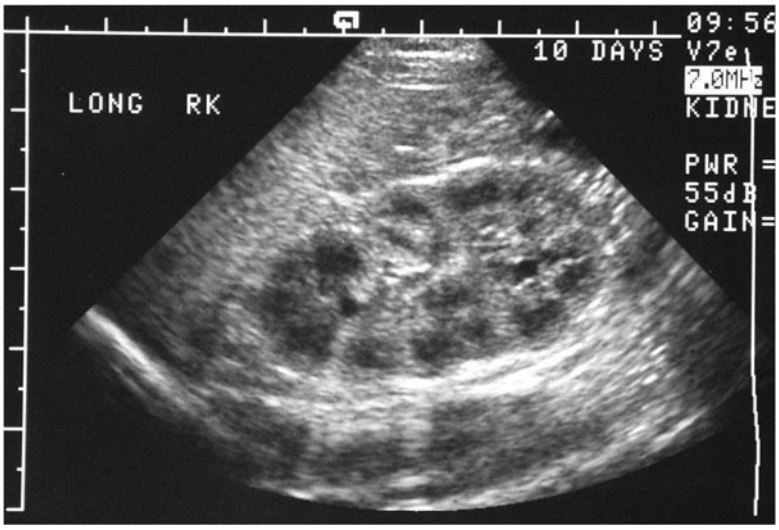

Fig. 2.1. Normal renal sonogram demonstrating reniform shape, parallel orientation to psoas major, central echogenic focus (correlates with pelvis, sinus fat, vasculature), surrounded by homogeneous parenchyma.

taken in both longitudinal and transverse views assessing renal length (compared against nomograms) (*5*), grade of hydronephrosis (using the Society for Fetal Urology grading system) (*6*), presence of any renal scarring, and the presence of duplication anomalies, cystic renal disease, and dilation of the proximal ureter. Bladder ultrasound should evaluate bladder volume and post-void residuals. It should also evaluate for such anomalies as ureteroceles, bladder masses, dilated distal ureters, or other pelvic abnormalities.

Scrotal ultrasound should include Doppler. In a child with scrotal pain, the study is limited by the fact that it is user-dependent and requires probe

placement over the painful area; however, it avoids radiation and is readily available. The study should be performed in the longitudinal and transverse plains to assess testicular symmetry and architecture. It will also evaluate the scrotum for extratesticular pathology.

Contrast VCUG: Contrast VCUG remains the preferred imaging study of the pediatric bladder. In most cases the VCUG (Fig. 2.2) provides excellent anatomic information as well as functional information on the bladder and urethra. The study starts with a plain film prior to catheterization that may detect sacral or bony abnormalities, spinal dysraphism, and abnormal bowel gas patterns and constipation. Following catheterization, contrast is instilled and an early anteroposterior film should be performed to assess for a ureterocele or bladder tumor. To evaluate for vesicoureteral reflux, steep oblique views of the bladder and renal fossae are taken just before and during voiding. Post-void images of the bladder will assess bladder emptying and urethral anomalies. The urethral catheter need not be removed during voiding (*7*).

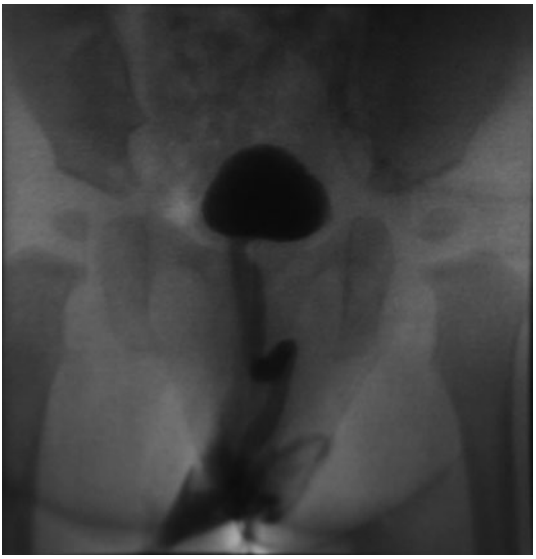

Fig. 2.2. Normal VCUG in a boy with smooth bladder, absence of reflux, normal urethra.

Nuclear Imaging

Kidney: There are two types of nuclear imaging of the kidney. Static renal scans assess abnormalities of the cortex such as infection and scarring using ^{99m}Tc-dimercaptosuccinyl acid (DMSA). Diuretic renography involves intravenous injection of a radiotracer that is reabsorbed by the tubules (MAG_3 or DTPA), timely injection of a diuretic (furosemide,

1 mg/kg), and bladder catheterization. Hydratation before the administration of the radiotracer prevents artificially poor tracer uptake. The split renal function is measured in the first 2 min. MAG_3 produces less background activity than DTPA and therefore is currently favored. Furosemide is typically administered at the peak of tracer uptake or at 20 min post-injection of tracer. The time needed for drainage of 50% of the tracer ($t^1/_2$) correlates with the obstructive state of the kidney. Standardization of this study has been proposed to best avoid many of the confounders of accurate interpretation (*8*).

Bladder: Radionuclide cystography provides limited information regarding bladder anatomy or function. Catheterization of the bladder is required and the tracer is instilled. Reflux can only be graded as mild, moderate, and severe. The utility of radionuclide cystography is limited relative to the contrast VCUG.

Scrotum: The blood flow to the testicles can be assessed by injecting 99mTc-pertechnetate intravenously and the testes evaluated in an immediate and delayed fashion.

ANOMALIES OF THE KIDNEY

Unilateral Renal Agenesis

The absence of a kidney is often suspected on prenatal sonogram, during evaluation of the urinary tract after infection, or incidentally during evaluation of other organ systems for non-urologic complaints. On plain film, loops of bowel will occupy the renal fossa. On ultrasound, the renal fossa will be empty and the adrenal gland in the normal position. The absence of functioning renal tissue in the abdomen or pelvis on DMSA, MR, or CT confirms the diagnosis. VCUG, either contrast or radionuclide, should be performed as vesicoureteral reflux is commonly seen in these cases (*9*).

Renal Ectopia

Kidneys develop in the bony pelvis and ascend during embryogenesis to their typical location in the flank. However, kidneys may be found in the pelvis (rarely the chest) or crossed to the contralateral side either fused or unfused. Ectopic kidneys can be detected on ultrasound (Fig. 2.3), IVU, CT, or MR. The horseshoe kidney, the most common fusion anomaly (Fig. 2.4), can be suspected when both kidneys are malrotated and caudally positioned on ultrasound, CT, or MR. Horseshoe kidneys are at risk for UPJ obstruction. The isthmus that separates the two kidneys may demonstrate function on nuclear scintigraphy (DMSA or MAG_3). Ultrasound should be performed regularly to screen for Wilms' tumor and followed by CT or MR if suspected.

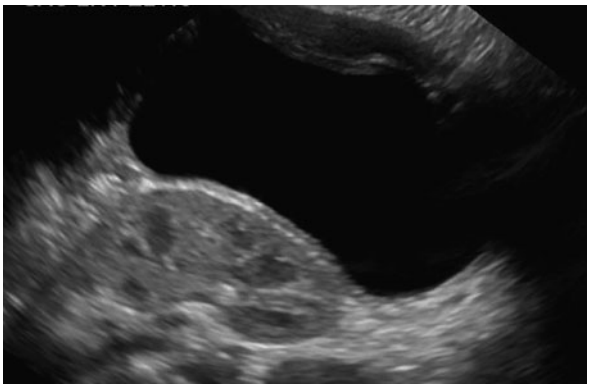

Fig. 2.3. Ectopic kidney located in the pelvis behind the bladder.

Fig. 2.4. Horseshoe kidney found in the pelvis with fusion of the lower poles.

Renal Cystic Diseases

Autosomal recessive polycystic kidney disease (ARPCD) – ultrasound is well suited to make the diagnosis of ARPCD. Both kidneys are reniform in shape but very large and hyperechoic. The ectatic dilated tubules create numerous interfaces that is responsible for the increased echogenicity.

Autosomal dominant polycystic kidney disease *(*ADPCK*)* – on ultrasound, ADPCK will demonstrate bilateral multiple renal cysts of variable size. In the early phase, the cysts are fewer in number and the parenchyma demonstrates normal corticomedullary differentiation and echogenicity. Later, the cysts grow and compress the renal parenchyma. Very large cysts

may distort the renal pelvis. MR or CT are best to assess hemorrhage into a cyst if there is suspicion on ultrasound.

Multicystic dysplastic kidney (MCDK) – The ultrasound findings in these cases include non-communicating multiple cysts of variable size and a paucity of renal parenchyma (Fig. 2.5). It can sometimes be challenging to distinguish MCDK from a severely hydronephrotic kidney. In MCDK, the largest cyst is not typically in the center and there will be no function on nuclear scintigraphy. Ultrasound can be used to follow children with MCDK as these cysts often involute and the renal unit contracts or disappears and to assess the contralateral kidney where abnormalities can be found in roughly 40%. VCUG is indicated to evaluate for vesicoureteral reflux into the stump of the MCDK or into the contralateral kidney (*10*).

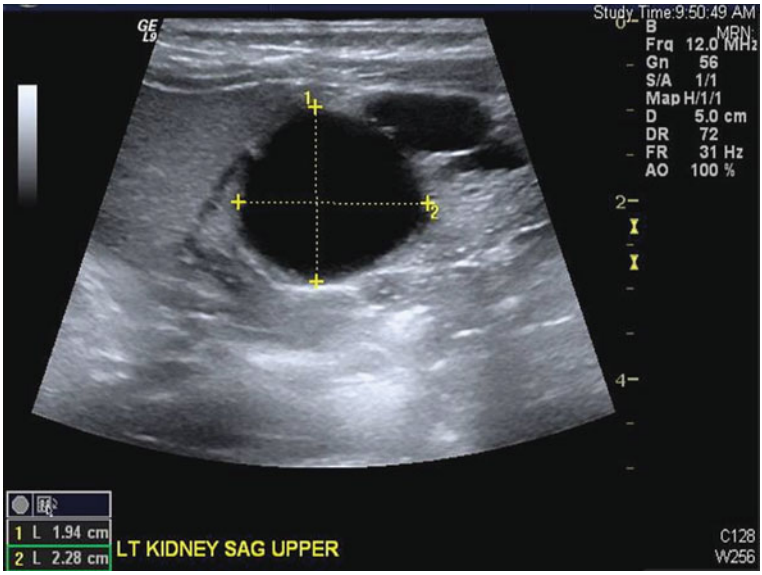

Fig. 2.5. Multicystic dysplastic kidney demonstrating multiple cystic structures that fail to communicate and the absence of normal parenchyma.

Hydronephrosis

The most common ultrasound finding in the kidney is hydronephrosis (*11*). Prenatally, the renal pelvis is measured in the anteroposterior dimension to assess the risk of a uropathy (*12*, *13*). Postnatally the presence of hydronephrosis is assessed using the Society for Fetal Urology Grading System (Fig. 2.6). By this system, the highest grade of hydronephrosis is associated with significant renal parenchymal thinning. It is important to distinguish hydronephrosis from the normal renal pyramids. Pyramids are small and ovoid or round hypoechoic areas that are radially distributed around the kidney.

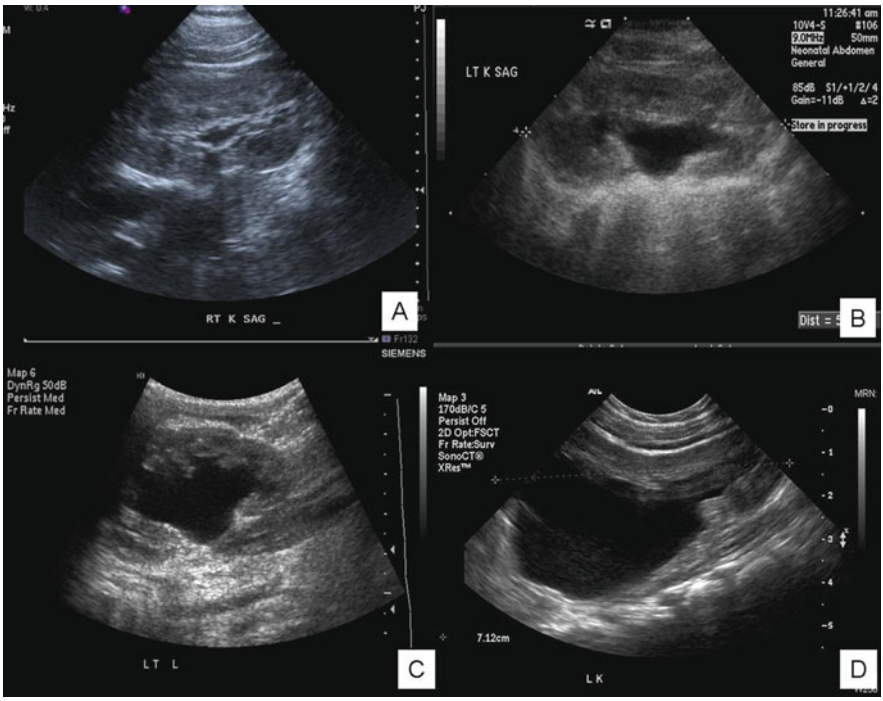

Fig. 2.6. Hydronephrosis according to the Society for Fetal Urology grading system: (**a**) 1-mild pelvic dilation, (**b**) 2-moderate pelvic dilation, (**c**) 3-dilation including calyces, normal parenchyma; (**d**) 4-calyceal dilation and parenchymal thinning.

Hydronephrosis can be primary or secondary. Primary hydronephrosis may obstructive or non-obstructive. Secondary hydronephrosis may result from many of the processes described below. The presence of hydronephrosis will often indicate a need for VCUG to detect vesicoureteral reflux, posterior urethral valves, or other pathology. Diuretic renography can be performed to assess for obstruction and to determine the split renal function. It is possible that MR may serve this role in the future (*2*, *14*).

Ureteropelvic Junction (UPJ) Obstruction

As mentioned earlier, hydronephrosis can be noted by several modalities such as US, CT, MR, and IVU. The Society of Fetal Urology Grading System (*6*) can be used to describe the extent of dilation. Pelvic dilation without extension into the calyces constitutes grades 1 and 2. Extension of hydronephrosis into the calyces defines grade 3 while thinning of parenchyma defines grade 4. When there is intermittent obstruction and flank pain, the grade of hydronephrosis may appear less impressive than expected (*15*).

The etiology of the hydronephrosis needs to be defined. VCUG will be performed to assess for vesicoureteral reflux. To determine if obstruction is present, the diuretic renogram using either MAG_3 or DTPA remains the gold standard. Standardization of the technique of this study has reduced the confounding variables associated with its interpretation and determination of split renal function and radiotracer washout following furosemide administration. A $t^1/_2$ value of >20 min and specific drainage curves establishes the presence of obstruction (Fig. 2.7).

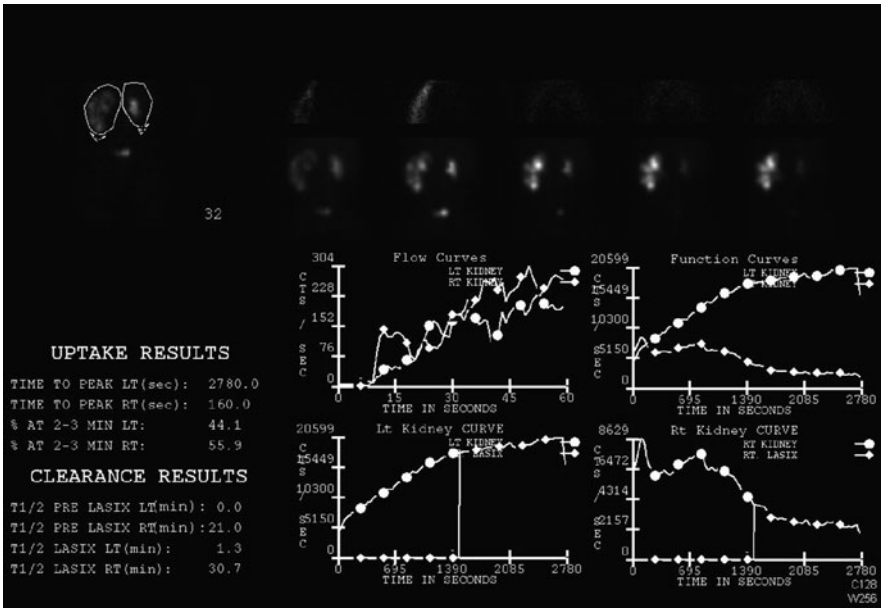

Fig. 2.7. Diuretic renogram with MAG3 demonstrating flat drainage after furosemide administration.

The etiology of obstruction differs in young children and older children. The younger children tend to be obstructed by an intrinsic narrowing of the ureter at the ureteropelvic junction. Older children and adults are often obstructed by vessels crossing anteriorly to the lower pole of the kidney causing impingement. Retrograde pyelography can establish the diagnosis as a linear filling defect. CT (*16*) with contrast or by MR may identify the vessels and their course.

Collecting System Duplication

Duplication of the renal collecting system is common and may be incomplete or complete (*17*). Most cases are inconsequential while others are associated with clinically significant anomalies such as ureterocele, ectopic ureters, ureteropelvic junction obstruction, or reflux. Duplications may be detected on prenatal ultrasound or postnatally following a clinical event.

Renal and bladder ultrasound can help detail the nature of the duplication. The kidney may reveal two central echogenic foci separated by a bar of renal parenchyma. The renal parenchyma may have normal echotexture or it may be hyperechoic due to dysplasia from reflux or obstruction. Hydronephrosis may or may not be present in either of the two collecting systems (Fig. 2.8). The bladder is normal in thickness, distension, and contour. The ureters may not be visible or may be visible proximally and/or distally.

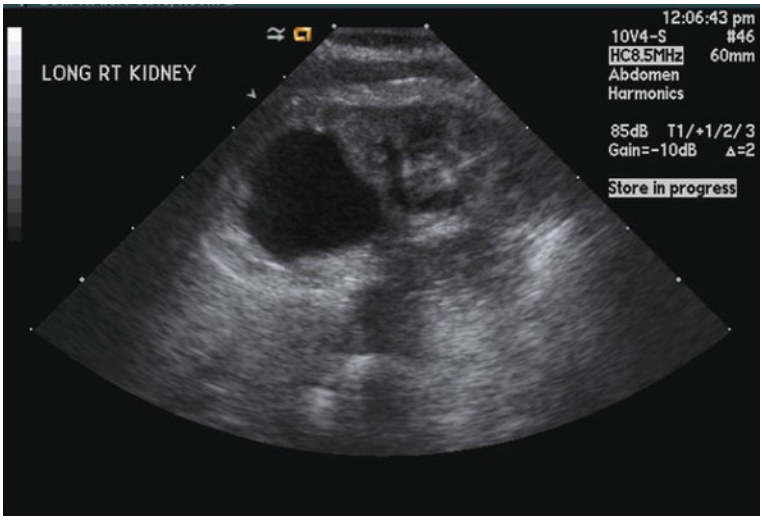

Fig. 2.8. Ultrasound of duplicated collecting system with hydronephrosis of the upper pole moiety.

The VCUG and diuretic renogram may be needed to provide additional diagnostic information. The lower pole system is more likely to be associated with vesicoureteral reflux (Fig. 2.9) that should be graded according to the International Grading System (*18*) as well as ureteropelvic junction obstruction. Obstruction at the level of the bladder from ureteral ectopia or ureterocele is more common in the upper pole system. The "drooping lily" is a classic finding on IVU, reflecting an obstructed upper pole duplication producing the downward and lateral displacement of the lower pole. VCUG should be performed using a non-ballooned catheter; dilute contrast and images during the early filling phase should detect a ureterocele or the location of an ectopic ureteral orifice and any associated reflux. Obstruction will be determined by the $t^1/_2$ and washout curve of a diuretic renogram.

Stones

The presence of renal or ureteral calculi is best seen on non-contrast CT or by ultrasound. Ultrasound is less useful in detecting small stones. Larger ones will appear as echogenic foci with posterior shadowing, which helps

Fig. 2.9. VCUG demonstrates vesicoureteral reflux into the lower pole collecting system without contrast in the upper pole.

to distinguish the stone from fat or blood vessels. Hydronephrosis behind the stone can often be seen. Non-contrast thin slice (3–5 mm) CT is the best imaging study to define the presence of stones (*19*). In addition, CT will accurately define stone location, size, number, and associated hydronephrosis. The speed of spiral CT precludes the need for sedation in most children. CT is also superior to ultrasound in documenting bladder stones especially in augmented bladders.

Pyelonephritis

Signs of renal inflammation can be detected on renal scintigraphy, MR, CT, and ultrasound. Static renal scintigraphy using ^{99m}Tc-dimercaptosuccinyl acid (DMSA) can detect cortical abnormalities such as infection and scarring. Images are acquired every 2–4 h in the anterior, posterior and oblique views (Fig. 2.10). The study needs to be repeated about

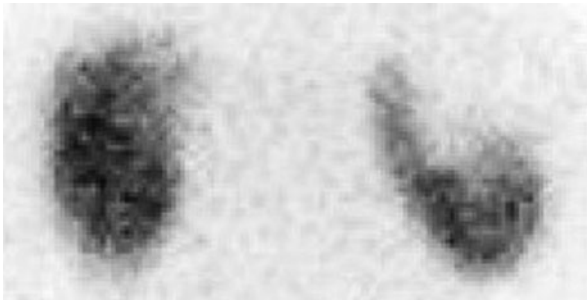

Fig. 2.10. DMSA scan of child with clinical pyelonephritis demonstrating poor uptake of tracer in the upper pole of the left kidney.

4 months later to differentiate cortical scarring from acute infection. MR may play a larger role in the future in making this distinction (*1*). On CT, there may be wedge-shaped segments of low attenuation radiating toward the surface from the collecting system, variable hydronephrosis, enlarged size, and delay in uptake of contrast. Similarly, ultrasound findings include enlarged size and heterogeneous echotexture from edema and pelvic dilation; these should resolve after treatment.

ANOMALIES OF THE URETERS

Megaureter

Megaureter is a wide ureter larger than 7 mm in diameter. The causes can be divided into refluxing, obstructive and non-refluxing, non-obstructive, or primary megaureter that corresponds to their radiographic findings. After ultrasound identifies the dilated ureter (Fig. 2.11), contrast VCUG will identify primary high-grade vesicoureteral reflux or secondary to posterior urethral valves, ureterocele, or neurogenic bladder dysfunction. When reflux is absent, obstruction will be evaluated by diuretic renogram ($t^1/_2 > 20$ min. In equivocal cases, IVU or MRU (*20*) or CT may offer greater anatomical detail revealing a congenital stricture, ureteral valve, or the location of an ectopic ureteral orifice.

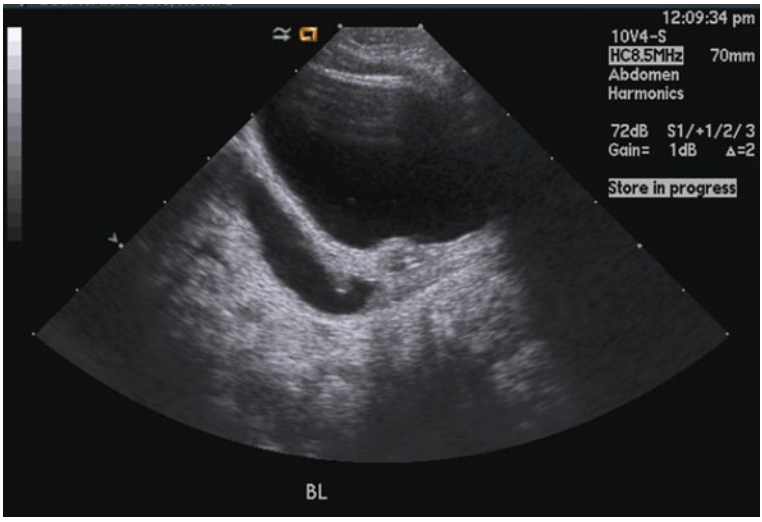

Fig. 2.11. Ultrasound of the bladder demonstrating elongated hypoechoic structure posteriorly consistent with dilated ureter.

Ureterocele

Proper imaging of the child with a ureterocele requires renal and bladder ultrasound, VCUG, and diuretic renography. This is true because ureteroceles may be associated with reflux, obstruction, and either single or duplicated collecting systems. Ultrasound (Fig. 2.12) is the most effective modality for identifying the presence of the ureterocele as a round thin-walled cystic structure at the base of the bladder; the size of the ureterocele is variable as is the amount of hydroureteronephrosis (*21*). The contralateral ureter may also be dilated if the ureterocele impinges on the contralateral orifice retarding urine passage or weakening the integrity of the antireflux mechanism, or obstructs the bladder outlet raising bladder pressures.

VCUG (Fig. 2.13) should be performed to better assess the ureterocele and its effect. Ureteroceles appears as filling defects, of variable size, within the bladder. The use of dilute contrast and early imaging are necessary to avoid obscuring the ureterocele with dense contrast or effacing the ureterocele by an over-distended bladder. The everting ureterocele is the one that appears to be outside of the bladder and may be misdiagnosed as a bladder diverticulum (*22*). Vesicoureteral reflux may be present in any ureter but is most likely to affect the ipsilateral lower pole system. Postoperative VCUG is important particularly following cystoscopic puncture where iatrogenic creation of reflux is the most common complication. Diuretic renography will determine the split renal function and the drainage patterns of all renal moieties. Each moiety should be considered a distinct region of interest.

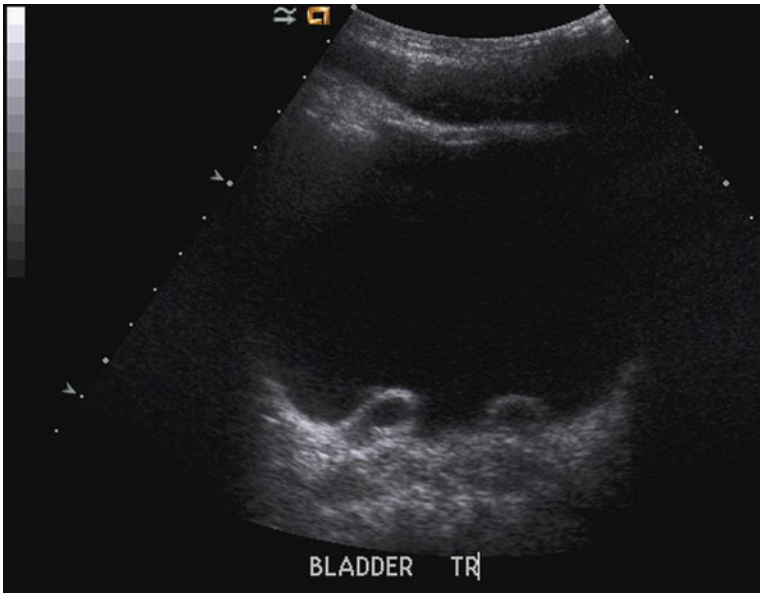

Fig. 2.12. Small bilateral ureteroceles seen on ultrasound along floor of the bladder.

Fig. 2.13. VCUG demonstrating moderate sized filling defect on the right side of the bladder consistent with a ureterocele.

Although performing an IVU is not commonplace today, two classic findings of ureteroceles are worthy of mention. The "cobra head" or "spring onion" findings reflect the radiolucent ureterocele wall surrounding the contrast-filled ureterocele. The "drooping lily" represents downward and lateral lower pole displacement by the hydronephrotic obstructed poorly functioning upper pole system.

ANOMALIES OF THE BLADDER

Vesicoureteral Reflux

Vesicoureteral reflux is diagnosed most commonly after hydronephrosis is detected prenatally or during the work up of a urinary tract infection. Ultrasound may demonstrate normal kidneys and ureters or various degrees of hydronephrosis or hydroureteronephrosis. The degree of hydronephrosis does not necessarily correlate with the grade of vesicoureteral reflux (*23*). The single or duplicated nature of the collecting system will also be assessed. The presence of cortical scarring associated with reflux and urinary tract infections is not well detected by ultrasound. If scarring is extensive, there may be an irregular renal contour, loss of corticomedullary differentiation, or a contracted kidney may be seen. DMSA and MR are superior studies to detect the presence of the scars and dysplasia. Ultrasound of the bladder likely shows a smooth walled bladder unless the child has posterior urethral valves or myelodysplasia where the bladders are considerably thickened. Dilated distal ureters may also be seen.

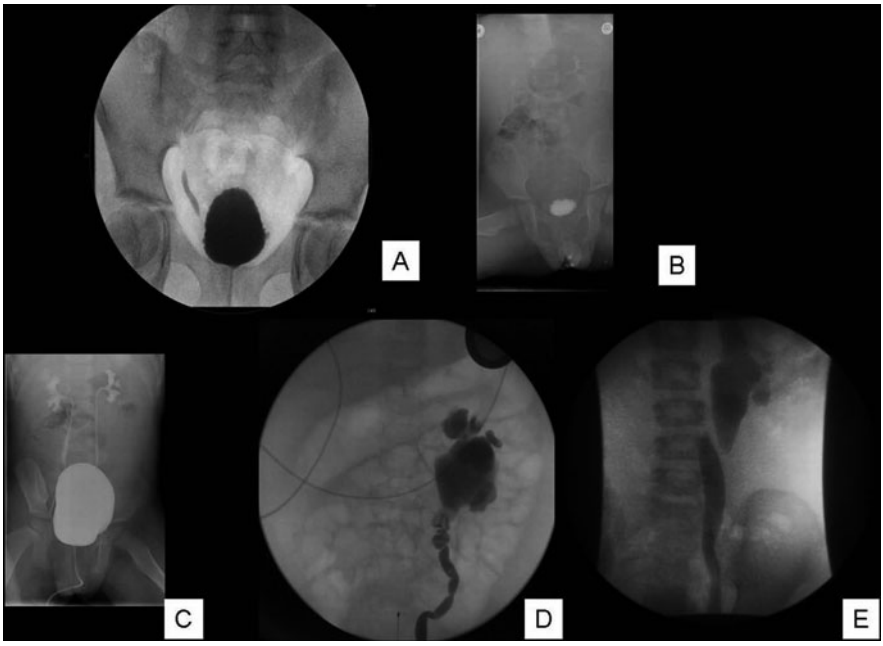

Fig. 2.14. Grades of vesicoureteral reflux according to the grading system of the International Reflux Study. (**a**) Grade 1 ureter only (**b**), Grade 2 into undilated pelvis (**c**), Grade 3 into mildly dilated pelvis, (**d**) Grade 4 into dilated calyces, and (**e**) Grade 5 into very dilated pelvis and blunting of all calyces.

Reflux should be graded after contrast VCUG (Fig. 2.14). Cyclical VCUG where the bladder is repeatedly filled and emptied may increase the sensitivity of the study to detect reflux. Grading is based on the International Reflux Study Grading System (I–V). Assessing the degree of ureteral dilation helps to plan for the need for ureteral tapering. The VCUG also evaluates the bladder for trabeculations, diverticulae, ureteroceles, and the urethral obstructive anomalies such as posterior urethral valves. Radionuclide VCUG (Fig. 2.15) is appropriate for use when the presence or absence of reflux is the only consideration, e.g., postoperatively, in follow-up of children on prophylactic antibiotics, and in screening of siblings without urologic complaints. The grading of reflux after radionuclide VCUG is less specific, i.e., mild, moderate, and severe.

Neurogenic Bladder

The neurogenic bladder is imaged by VCUG and ultrasound. The plain film taken at the beginning of a VCUG may demonstrate the spinal abnormality responsible for the neurogenic bladder. The infusion of contrast will fill the trabeculations, sacculations, and diverticulae. The "Christmas Tree" bladder (Fig. 2.16) from severe bladder hypertonicity is characterized by a vertical orientation and multiple diverticulae. Any associated reflux will

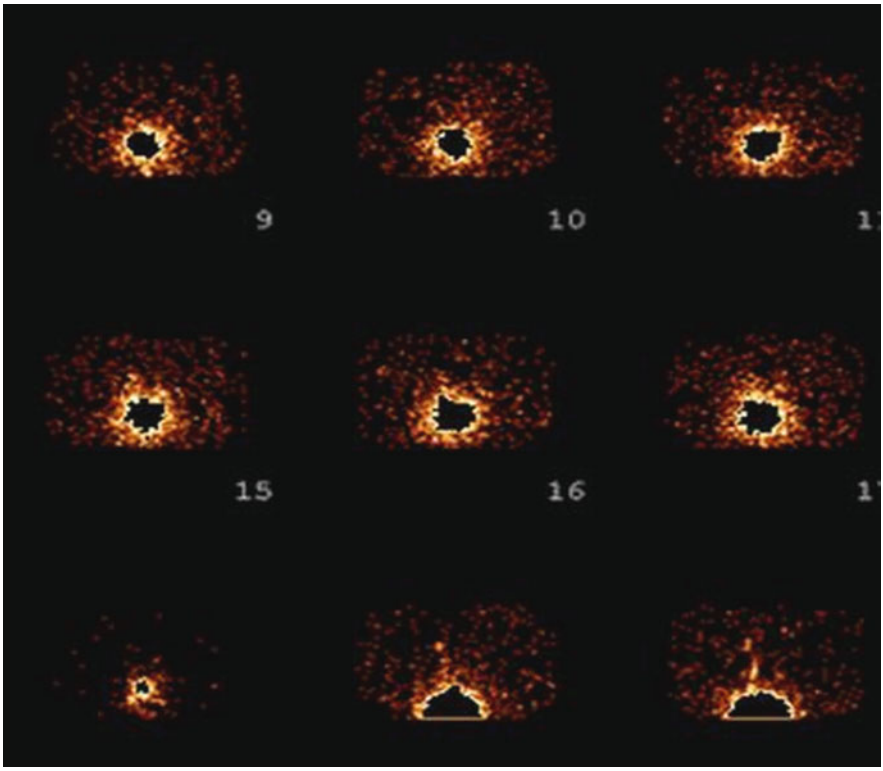

Fig. 2.15. Radionuclide cystogram demonstrates tracer only the bladder.

Fig. 2.16. VCUG from child with neurogenic bladder demonstrating elongation, diverticulae, and cellules – "Christmas Tree bladder."

be detected. An ultrasound will demonstrate bladder wall thickening, associated hydronephrosis or hydroureteronephrosis from reflux, or elevated bladder pressure. The ability of the bladder to empty can be assessed by identifying the extent of post-void residual.

Bladder Diverticulum

Bladder diverticulae occur in various settings and are best assessed by VCUG (*24*). Congenital out-pouching occurs posteriorly and are variable in size but may become larger than the bladder (Fig. 2.17). Paraureteral

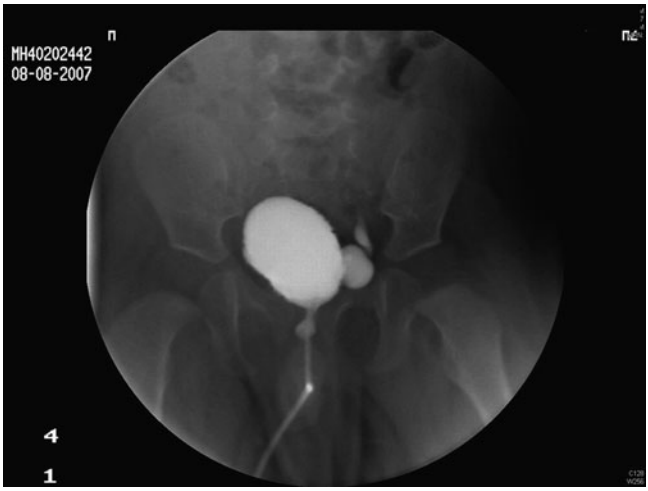

Fig. 2.17. VCUG showing moderate sized diverticulum posterior to the bladder.

Fig. 2.18. Post-void image from a VCUG demonstrating bilateral Hutch, paraureteral bladder diverticulum in child with vesicoureteral.

(Hutch) diverticulae are also congenital and variable in size but may lead to reflux or prevent its spontaneous resolution (Fig. 2.18). As mentioned above, bladder outlet obstruction or neurogenic dysfunction may lead to multiple diverticulae reflecting high bladder pressures. Ultrasound may demonstrate bladder wall thickening but can miss identifying diverticulae unless they are substantially larger. There will be a hypoechoic area in the pelvis that may demonstrate its communication with the bladder. It may be difficult to distinguish very large diverticulae from the bladder itself. In the case of large diverticulae, anatomical considerations can be made as well as an assessment of the emptying of the diverticulum (Fig. 2.16).

ANOMALIES OF THE URETHRA

Posterior Urethral Valves (PUV)

Posterior urethral valves can lead to variable detriment to both the lower and upper urinary tracts. The point along the spectrum can be well-defined using the combination of renal and bladder ultrasound, VCUG, and nuclear scintigraphy. On ultrasound, hydronephrosis of all grades or hydroureteronephrosis may be seen. In the presence of severe renal damage, ultrasound may reveal parenchyma that is hypoechoic and sustained thinning as well as loss of corticomedullary differentiation, or cystic changes. The ureters will demonstrate variable amount of hydroureter. Bladder wall thickening from detrusor hypertrophy is commonly seen. On prenatal ultrasound, oligohydramnios can be seen in addition to hydronephrosis, normal to hyperechoic renal echotexture, hydroureter, thick walled bladder, and a dilated prostatic urethra (*25*).

While posterior urethral valves may be suspected on ultrasound, the diagnosis is made by contrast VCUG (Fig. 2.19). The more common findings in the bladder and urethra includes trabeculations and saccules or diverticulae, a narrow bladder neck due to bladder neck muscular hypertrophy, a dilated and elongated posterior urethra, and an abrupt change in caliber at the external sphincter. Vesicoureteral reflux of any grade with possibly exaggerated dilation and tortuosity of the ureters may be present.

The role of diuretic renography is to provide information regarding differential renal function and urinary drainage. Of these bladders are associated with high bladder pressures and reflux that would cause considerable artifact such as retarded drainage; therefore, the insertion of a urethral catheter is crucial for this study.

When there are urine collections outside of the kidney secondary to forniceal rupture, ultrasound or CT are excellent imaging studies.

Other Urethral Anomalies

Anterior urethral valve: Anterior urethral valves are not common but can cause obstruction of the urinary tract. In contrast to posterior urethral valves that are limited to the area of the prostatomembranous portion of the urethra,

Fig. 2.19. VCUG in a neonate demonstrating irregular shaped bladder with dilated posterior urethra and sudden change in caliber at the location of the valve and vesicoureteral reflux into dilated ureters.

anterior urethral valves may be found in the penoscrotal, bulbar, or penile portion (anterior urethra). To best define the location and extent of obstruction and associated reflux, a VCUG is best performed. The anterior urethral valve typically appears as a linear filling defect ventrally with urethral dilation proximally and a narrowing distally or as an abrupt change in caliber. At times, the valve will appear as urethral dilation into a smooth bulge within the urethra. Ultrasound can be normal or demonstrate considerable hydroureteronephrosis depending on the obstructive nature of the valve.

Megalourethra: This uncommon anomaly may be divided into scaphoid or fusiform types. The scaphoid variant is more common and is due to deficiency of the corpora spongiosum. On VCUG, it appears as boat-like urethral dilation. The less common fusiform variant is due to deficiency of corpora cavernosum and it appears as a long floppy dilated urethra on VCUG.

Prostatic utricle: The utricle is a midline out-pouching arising in the area of the verumontanum and represent Mullerian system remnants. Infection may arise in either the urine or in the genital duct system. This will lead to imaging and detection of the utricle on VCUG. These are typically small but can be large and can be better defined using CT or MR.

ANOMALIES OF THE TESTIS

Acute Testicular Pain

The general urologist is well acquainted with the most common causes of acute testicular or scrotal pain: testicular torsion, appendage torsion, and

epididymal inflammation. The mainstay of imaging children with pain in the scrotum is ultrasound with Doppler and nuclear scintigraphy.

Ultrasound (Fig. 2.20) is best at defining the combination of symmetry, architecture, and perfusion of the testicles. The technique was described early in this chapter. The study should start on the non-painful testis and then used to compare with the symptomatic side. The sonographic features of testicular torsion includes heterogeneity of the parenchyma associated with non-viability (*26*) (Fig. 2.21), echogenic parenchyma without detectable Doppler flow. The inflamed testis may also demonstrate a heterogeneous appearance but there will be ample flow or hyperperfusion of the testis and epididymis. Associated reactive hydroceles may be present with either diagnosis.

Nuclear scintigraphy using 99mTc-pertechnetate cannot provide architectural information but effectively assesses testicular blood flow to both testes (Fig. 2.22). Symmetric activity reflects symmetric blood flow and excludes testicular torsion except in the case of intermittent torsion. When there is increased activity to the symptomatic testis, the diagnosis is likely epididymitis, orchitis, or inflammation secondary to torsion of an appendage. When there is acute testicular torsion, there will be absence of activity when compared with the unaffected side. The "donut sign" associated with missed torsion reflects a hyperemic rim of flow around a central area without tracer uptake.

Fig. 2.20. Transverse view of the scrotum showing both testes; the *left* has absent flow to the testis while the *right* one shows considerable Doppler signals.

Fig. 2.21. Ultrasound of the testis that has clinical history of acute pain from presumed torsion of 48 h duration. Heterogeneity of the parenchyma is clearly seen and is consistent with necrosis seen at the time of surgery.

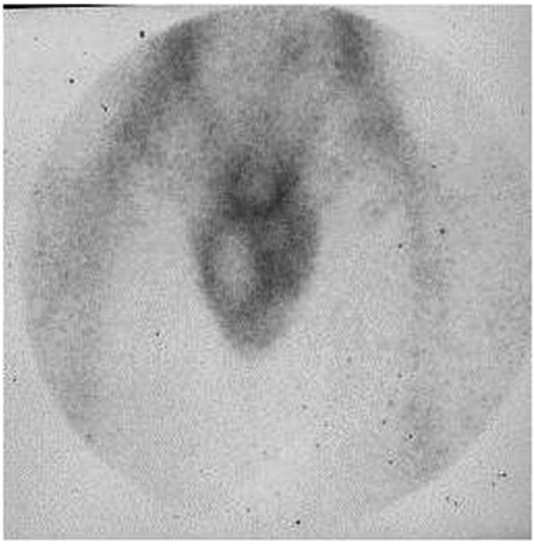

Fig. 2.22. Nuclear scintigraphy of patient with acute onset of scrotal pain demonstrating absence of activity on the *right* side. The *left* side shows normal activity. Torsion of the testis was discovered at surgery.

CONCLUSION

Any urologist treating children needs to have comfort with the proper imaging of the genitourinary tract. This comfort includes ordering the proper studies as well as their interpretation. The mainstay of imaging remains ultrasound, VCUG, and nuclear scintigraphy. With these three studies, the management of most congenital and acquired abnormalities of the genitorurinary tract should be facilitated. While ultrasound is free of ionizing radiation, the other two studies are not without risk and are invasive in nature. However, advances in CT and MR may lead to future paradigm shifts that make imaging faster, more detailed, and free of radiation.

REFERENCES

1. Weiser, A.C., Amukele, S.A., Leonidas, J.C., Palmer, L.S. (2003) The role of gadolinium enhanced magnetic resonance imaging for children with suspected acute pyelonephritis. J Urol 169:2308–11
2. Jones, R.A., Perez-Brayfield, M.R., Kirsch, A.J., Grattan-Smith, J.D. (2004) Renal transit time with MR urography in children. Radiology 233:41–50
3. Giorgi, L.J. Jr., Bratslavsky, G., Kogan, B.A. (2005) Febrile urinary tract infections in infants: renal ultrasound remains necessary. J Urol 173:568–70
4. Siegel, M.J. (1997) The acute scrotum. Radiol Clin North Am 35:959–76
5. Rosenbaum, D.M., Korngold, E., Teele, R.L. (1984) Sonographic assessment of renal length in normal children. AJR Am J Roentgenol 142:467–9
6. Fernbach, S.K., Maizels, M., Conway, J.J. (1993) Ultrasound grading of hydronephrosis: introduction to the system used by the Society for Fetal Urology. Pediatr Radiol 23: 478–80
7. Fernbach, S.K., Feinstein, K.A., Schmidt, M.B. (2000) Pediatric voiding cystourethrography: a pictorial guide. Radiographics 20:155–68
8. Conway, J.J., Maizels, M. (1992) The "well tempered" diuretic renogram: a standard method to examine the asymptomatic neonate with hydronephrosis or hydroureteronephrosis. A report from combined meetings of The Society for Fetal Urology and members of The Pediatric Nuclear Medicine Council – The Society of Nuclear Medicine. J Nucl Med 33:2047–51
9. Cascio, S., Paran, S., Puri, P. (1999) Associated urological anomalies in children with unilateral renal agenesis. J Urol 162:1081–3
10. Damen-Elias, H.A., Stoutenbeek, P.H., Visser, G.H., Nikkels, P.G., de Jong, T.P. (2005) Concomitant anomalies in 100 children with unilateral multicystic kidney. Ultrasound Obstet Gynecol 5:384–8
11. Mandell, J., Blyth, B.R., Peters, C.A., Retik, A.B., Estroff, J.A., Benacerraf, B.R. (1991) Structural genitourinary defects detected in utero. Radiology 178:193–6
12. Ismaili, K., Hall, M., Donner, C., Thomas, D., Vermeylen, D., Avni, F.E. (2003) Brussels Free University Perinatal Nephrology study group. Results of systematic screening for minor degrees of fetal renal pelvis dilatation in an unselected population. Am J Obstet Gynecol 188:242–6
13. Odibo, A.O., Raab, E., Elovitz, M., Merrill, J.D., Macones, G.A. (2004) Prenatal mild pyelectasis: evaluating the thresholds of renal pelvic diameter associated with normal postnatal renal function. J Ultrasound Med 23:513–7
14. Grattan-Smith, J.D., Perez-Bayfield, M.R., Jones, R.A., Little, S., Broecker, B., Smith, E.A., Scherz, H.C., Kirsch, A.J. (2003) MR imaging of kidneys: functional evaluation using F-15 perfusion imaging Pediatr Radiol 33:293–304
15. Rooks, V.J., Lebowitz, R.L. (2001) Extrinsic ureteropelvic junction obstruction from a crossing renal vessel: demography and imaging. Pediatr Radiol 31:120–4

16. Mitsumori, A., Yasui, K., Akaki, S., Togami, I., Joja, I., Hashimoto, H., Kumon, H., Hiraki, Y. (2000) Evaluation of crossing vessels in patients with ureteropelvic junction obstruction by means of helical CT. Radiographics 20:1383–93
17. Campbell, M.F. (1970) Anomalies of the ureter. In Campbell MF, Harrison JH, eds. Urology, 3rd ed, Philadelphia, WB Saunders Company, p. 1512
18. Lebowitz, R.L., Olbing, H., Parkkulainen, K.V., Smellie, J.M., Tamminen-Moebius, T.E. (1985) International system of radiographic grading of vesicoureteric reflux. Pediatr Radiol 15:105–9
19. Palmer, J.S., Donaher, E.R., O'Riordan, M.A., Dell, K.M. (2005) Diagnosis of Pediatric Urolithiasis: Role of Ultrasonography and CT Scan. J Urol 174:1413–6
20. Wille, S., von Knobloch, R., Klose, K.J., Heidenreich, A., Hofmann, R. (2003) Magnetic resonance urography in pediatric urology. Scand J Urol Nephrol 37:16–21
21. Cremin, B.J. (1986) A review of the ultrasonic appearances of posterior urethral valve and ureteroceles. Pediatr Radiol 16:357–64
22. Zerin, J.M., Baker, D.R., Casale, J.A. (2000) Single-system ureteroceles in infants and children: imaging features. Pediatr Radiol 30:139–46
23. Blane, C.E., DiPietro, M.A., Zerin, J.M., Sedman, A.B., Bloom, D.A. (1993) Renal sonography is not a reliable screening examination for vesicoureteral reflux. J Urol 150:752–5
24. Blane, C.E., Zerin, J.M., Bloom, D.A. (1994) Bladder diverticula in children. Radiology 190:695–7
25. Dinneen, M.D., Dhillon, H.K., Ward, H.C., Duffy, P.G., Ransley, P.G. (1993) Antenatal diagnosis of posterior urethral valves. Br J Urol 72:364–9
26. Kaye, J.D., Levitt, S.B., Gitlin, J.S., Friedman, S.C., Freyle, J., Palmer, L.S. (2008) Parenchymal echotexture predicts testicular salvage after torsion – a new paradigm to determine the need for emergent exploration. J Urol 180(4 Suppl):1733–6

3 Urinary Tract Infections

Hans G. Pohl, Sherry Sedberry-Ross, and H. Gil Rushton

Abstract When children present with a urinary tract infection (UTI), the goal is early recognition and treatment in an attempt to prevent renal parenchymal damage and subsequent renal scarring. The risks of these events are greatest during infancy. However, a delay in diagnosis and treatment of acute pyelonephritis (APN) can result in scarring at any age. In cases of recurrent pyelonephritis, progressive damage to the kidney can occur (Jakobsson et al., Arch Dis Child 70:111, 1994; Jakobsson et al., Pediatr Nephrol 6:; 328, 1992 *)*. Renal cortical scarring can result in long-term sequelae including uremia, hypertension, in girls, toxemia of pregnancy and in severe cases, end-stage renal disease. Since renal scarring is the fourth leading cause of renal transplantation in children, the need for early diagnosis, treatment, and evaluation of children with UTIs is significant.

Keywords Urinary tract infections · Acute pyelonephritis · DMSA renal scintigraphy · Vesicoureteral reflux · Dysfunctional elimination

INTRODUCTION

The goal of current practice is the early detection of urinary tract pathology and prevention of renal infection by medical or surgical means. The now arcane concept that vesicoureteral reflux (VUR) predisposes the individual to renal scarring by a "water-hammer" effect has been supplanted by recognition of the primary role of urinary infection in the development of acquired renal scars and that renal damage associated with severe VUR may also be congenital. Prospective studies of children hospitalized with pyelonephritis proven by $^{99\text{-M}}$Tc-DMSA renal scans have shown that many of these children do not have VUR and that renal scarring can occur both in the presence and absence of demonstrable VUR (*1–4*). The risk of scarring is greatest in infancy, may be increased by a delay in diagnosis and treatment, and may be a progressive phenomenon associated with recurrent

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pyelonephritis (*1*, *5*, *6*). Long-term follow-up into adulthood of girls with significant renal scarring has demonstrated up to a 10% incidence of uremia, 13% incidence of hypertension, and a 13% incidence of toxemia of pregnancy (*7*). When one considers that renal scarring is the fourth leading cause for renal transplantation in children, the need for prevention becomes obvious (*8*).

EPIDEMIOLOGY

Urinary tract infection (UTI) is the second most common bacterial infection in children, with acute upper respiratory tract infections being more common. *Occult bacteriuria occurs in all age groups, but declines with increasing age, suggesting a maturation process. Uncircumcised infant boys are more susceptible to occult bacteriuria than girls. However, the male to female predominance in the first year of life is reversed in subsequent age groups* (*9*). The incidence of occult bacteriuria in children aged 5–10 years is between 1 and 1.7%, being most common in girls (*10*, *11*). It has been estimated that symptomatic urinary infections will affect 1.1% of boys and 3% of girls before the age of 11 years, but actual prevalence rates may be as high as 1.6 and 7.8%, respectively (*12*, *13*) (Fig. 3.1). Infants with symptomatic urinary infections are at risk for recurrent infection (26%), usually in the first 3 months of follow-up. In older girls the risk for recurrence following urinary infection is as high as 40–60% (*14*).

The greater risk of urinary infection in susceptible children persists into adulthood. In one study, 60 girls with childhood bacteriuria followed into adulthood (9–18 year follow-up) were compared with 38 healthy controls. A significantly greater incidence of bacteriuria of pregnancy was found in the study group (63.8%) when compared to the controls (26.7%). Interestingly, the propensity for urinary infection persisted in the children born to women with bacteriuria, whereas none of the children born to healthy controls demonstrated urinary infection (*15*).

The diagnosis of urinary infection in children may be hampered by the protean nature of the presentation, especially in infants. However, *high fever has been noted in half of the infant girls and in two-thirds of the boys with symptomatic urinary infections* (*13*). Hoberman et al. reviewed the prevalence of urinary tract infection in febrile infants (temperature >38°C) (*16*). Urine culture confirmed urinary infection in up to 5.9%. Infants with no apparent source of fever on clinical exam were twice as likely to have positive urine cultures as those infants with a suspicious exam (7.5% versus 3.5%, respectively). A significant number of children with febrile urinary tract infections are assessed as "well-appearing," at times resulting in a delay in appropriate management (*17*).

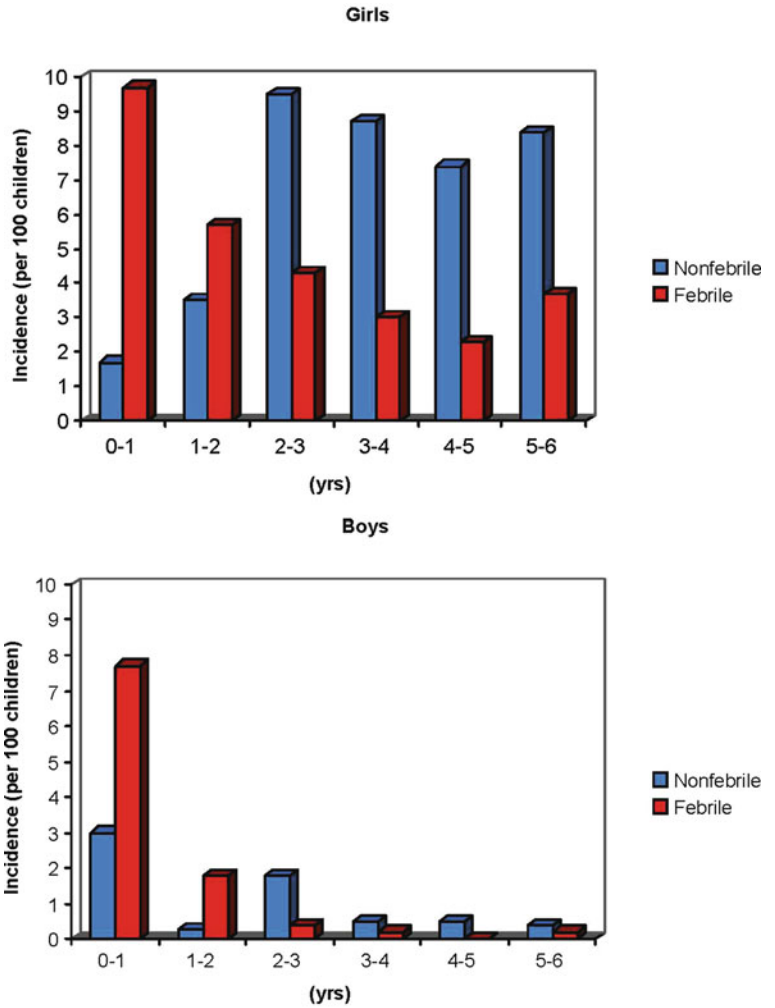

Fig. 3.1. Incidence of febrile and non-febrile urinary tract infection in boys and girls. Adapted from Winberg et al. Acta Pediatrc Scand, 1974.

ETIOLOGY

Enterobacteriacea, including *Escherichia coli*, *Klebsiella sp.*, *Proteus sp.*, *Pseudomonas sp.*, and enterococci, are the most common organisms invading the urinary tract (>95%). The bacteriological findings in the Goteburg study suggest that the environmental conditions in the periurethral region and the host defense mechanisms vary with age and sex (*12*). This study identified four characteristic trends in childhood urinary tract infections: (*1*) a high frequency of *Proteus* infections in older boys (most of whom were uncircumcised), and greater variability in infecting organisms in boys

than in girls; (*2*) a greater likelihood of staphylococcal infection in adolescence, especially in girls; (*3*) a greater frequency of *E. coli* urinary infection in neonatal boys than in girls of that age; and (*4*) a decreased frequency of *Klebsiella* urinary infection in older children (*12*). Sometimes the strain of bacterium is suggestive of underlying urinary pathology, such as the relationship of *Proteus sp.* and struvite stones.

BACTERIAL VIRULENCE FACTORS

Endotoxin, capsular antigens, alpha-hemolysin production, aerobactin production, and the presence of P-fimbria have all been identified as important factors in determining a strain's ability to propagate infection (*18*, *19*). *Endotoxin*, a lipopolysaccharide present in the bacterium's cell wall, is responsible for initiating the acute inflammatory response common to gram-negative infections. This same inflammatory response that eradicates bacteria may also lead to post-pyelonephritic scarring. *K-capsular antigens* enhance bacterial virulence by increasing resistance to phagocytosis by polymorphonuclear leukocytes. *Hemolysin* facilitates tissue invasion by digesting cells surrounding the site of bacterial adherence. Blanco et al. identified a greater incidence of in vitro alpha-hemolysin production in strains from children with acute pyelonephritis than in children with cystitis or asymptomatic bacteriuria (*19*). Despite the more invasive nature of hemolysin-producing *E. coli*, the presence of hemolysin does not necessarily portend a greater parenchymal inflammatory response, as is the case with endotoxin (*20*). *Aerobactin*, another recognized virulence factor, helps to support bacterial growth by chelating iron in the iron-poor urinary environment. Winberg et al.'s hypothesis that environmental and host factors change with advancing age is supported by the higher incidence of hemolytic strains and lower incidence of aerobactin-positive and P-fimbriated strains in adult men with acute pyelonephritis than is commonly seen in children (*21*).

The presence of *cell surface adhesion molecules* has been extensively investigated. Perineal colonization by uropathogenic bacteria has been found to precede clinical UTI in women and in children at risk for UTI (*21*–*25*). Uropathogenic bacteria, especially *E. coli*, employ appendages to adhere to human epithelial cells and thereby promote colonization. Collectively known as *fimbria*, these attachment structures exist as multiple types that are capable of recognizing and attaching to receptors located on uroepithelial cells (bacterial tropism).

P-fimbria, named for their ability to agglutinate red blood cells of the P-1 blood group, have been implicated as a virulence factor, which enhances colonization of the upper urinary tract. P-fimbria recognize and adhere to a specific carbohydrate moiety (alpha-D-galactopyranosyl-(1–4)-beta-D-galactopyranoside) located on the surface of uroepithelial cells. The ability of these bacteria to attach to urothelium provides a mechanism for the bacteria to colonize and ascend into the upper urinary tract even in

the absence of VUR. *Thus the presence of P-fimbria on the capsule of E. coli is thought to be an important etiologic contributor to non-reflux pyelonephritis.* In an early review of 49 female patients with cystitis or acute pyelonephritis, strains associated with pyelonephritis were more likely to adhere strongly to normal human urinary tract epithelial cells in culture (*26*). Subsequently, Kallenius et al. compared 35 children with non-obstructive acute pyelonephritis to 26 children with cystitis and 36 with asymptomatic bacilluria. P-fimbriated *E. coli* were identified in 91% of the children with pyelonephritis as compared to 19% with cystitis and 14% of those with asymptomatic bacilluria. The frequency of P-fimbriated *E. coli* in fecal isolates from healthy controls was even lower (7%) (*27*). However, in another study of children with febrile UTIs, no significant association was demonstrated between the occurrence of acute pyelonephritic changes on DMSA scintigraphy and the presence of specific virulence factors including P-fimbria. It was concluded that P-fimbriae were important for the development of systemic febrile infection regardless of the presence of renal parenchymal involvement, perhaps by facilitating the delivery of endotoxin through the uroepithelial lining of the upper urinary tract (*28*).

HOST DEFENSE AND RISK FACTORS

Perineal Factors

Hematogenous seeding of the urinary tract, despite the historical perception of its significance, is an uncommon source of urinary infection. When this is the cause of a renal infection, a cortical abscess rather than classic pyelonephritis occurs. Perineal colonization by intestinal flora is the putative source of most primary and recurrent urinary infections. In the female, colonization of the introitus occurs by epithelial attachment of bacteria, while in the male preputial epithelium serves as a niche (*29*). An infant's initial exposure to uropathogenic bacteria occurs at the time of birth (*30*) subjecting infants born to bacilluric mothers to a fourfold greater risk of urinary tract infections (*31*). Ultimately, the infant's own intestinal tract may become colonized by bacteria with uropathogenic potential (*32*, *33*).

Further evidence supporting the fact that most UTIs are ascending infections which begin with peri-meatal colonization is the increased incidence of urinary tract infection in uncircumcised boys compared with circumcised boys and girls during the first 6 months of life. This occurs despite the protective effect derived from the longer male urethral length (*34*). Winberg et al. first recognized the prevalence of preputial colonization in infant boys (*12*), noting that it persists to the age of 5 years (*35*). Others subsequently noted that greater than 95% of boys at risk for pyelonephritis are uncircumcised (*34*). Wiswell et al. documented that *the risk of pyelonephritis was ten times greater in the uncircumcised infant than in boys circumcised at birth* (*36*). Rushton and Majd prospectively found that 92% of boys under

6 months of age with febrile UTIs were uncircumcised, compared to 49% of a control group of boys with febrile URIs. The majority of these uncircumcised boys with febrile UTIs had DMSA scan proven pyelonephritis yet only 15% had VUR (*37*).

In girls the short urethra appears to be the most obvious explanation for the increased relative incidence of UTIs in girls as compared to boys past the first 6–12 months of life. Narrowed urethral caliber, historically blamed as the pre-eminent factor influencing susceptibility to lower UTIs in girls, does not play a role. It has long been established that the intrinsic urethral luminal size is not significantly smaller in those girls who are bacilluric compared with those who have never been infected. *Other commonly held misconceptions related to the etiology of UTIs in children are that improper wiping techniques and bubble baths predispose to urinary infections. There is no documented evidence to support these myths*. In fact, the strongest argument against improper wiping techniques being a cause of lower UTIs is that over 95% of non-toilet trained infants never develop urinary infection despite daily exposure to diapers soiled with feces. Although bubble baths may occassionally cause dysuria from local meatal or vaginal irritation, there is no documented association with bacterial cystitis.

Lower Urinary Tract Factors

Elimination disorders frequently complicate the interaction between pathogenic organisms and the uroepithelium of children at risk for urinary tract infections. Children may present with a broad spectrum of symptom severity with some symptoms elicited only by rigorous history taking. *Common voiding disorders in children prone to UTI range from the small capacity, unstable bladder characterized by frequency, urgency, posturing and wetting to the infrequent voider ("lazy bladder syndrome") characterized by very infrequent voiding, a large capacity bladder, paradoxical incontinence (wet despite a large bladder capacity), and constipation*. The importance of addressing voiding dysfunction in children with a history of urinary tract infection is suggested by data reporting that the incidence of UTI and VUR is decreased by successful management of voiding abnormalities in these children (*38–40*). *Two symptom complexes not associated with an increased risk of urinary tract infections are isolated primary nocturnal enuresis and the daytime urgency-frequency syndrome*.

Paramount to identifying the dysfunctional voider is a thorough voiding history. Squatting, delayed or infrequent micturition, urgency, constipation, and/or encopresis are significant and can be frequently elicited during evaluation of the child with urinary tract infection (50–94%) (*38*, *40–46*). Hellstrom et al. reported an abnormal voiding history in up to 49% of girls presenting between 3 and 5 years of age with their first urinary tract infection. Specifically, *the presence of daytime urinary symptoms strongly correlated with the risk for subsequent infection* (*47*). In a related study of

the same children, Hansson found that a majority of girls with "covert" bacilluria had urodynamic evidence of dysfunctional bladders when compared to controls (*48*) Wan et al. evaluated the relationship between toileting habits and anatomic abnormalities which predispose to infection in 101 children with UTI (77 girls and 24 boys). Ninety percent of the children without structural abnormalities demonstrated dysfunctional elimination as a contributing factor to their urinary infections, compared with 40% of those patients found to have a structural abnormality, such as VUR (*49*). *Fecal as well as urinary elimination is often impaired* (*50*) *and treatment of constipation has been found to correlate with resolution of urinary infection* (*51*).

A validated questionnaire has been developed in an effort to standardize the evaluation of children presenting with UTI and dysfunctional elimination as its etiology (*52*) (Table 3.1). This dysfunctional voiding scoring system resembles the International Prostate Symptom Score (I-PSS) in that it is self-administered means of quantifying the urinary and fecal symptoms present at diagnosis, and thus, provides a means for longitudinal assessment of treatments (*53*). Bartkowski and Doubrava (2004) have found the sensitivity of this tool lacking when compared against more objective measures of bladder function such as post void residual urine volume, uroflowmetry patterns, and EMG tracings (*54*). Until more robust quantitative tools become available, the DVSS provides a concise method by which to consider whether behavioral modification should be instituted in order to diminish the risk for recurrent UTIs.

Upper Urinary Tract Factors

The presence of vesicoureteral reflux, particularly moderate and severe grades, significantly enhances the likelihood that infecting organisms will access the renal parenchyma. In a prospective study of children with febrile UTIs evaluated by DMSA renal scans, children with moderate and severe reflux (grade III–V) were twice as likely to demonstrate acute parenchymal inflammatory damage compared with patients with mild or no VUR (*3*). When VUR is present, 80–90% of patients with febrile UTIs have acute abnormalities on DMSA scans, including almost all with grades III or higher VUR (*55*). *Vesicoureteral reflux compensates for the lack of specific bacterial virulence factors. In the presence of VUR adherence properties are not required for bacteria to gain access to the upper urinary tract. As a result, less virulent organisms are more often isolated from patients with reflux pyelonephritis* (*56*). *Despite the importance of moderate and severe reflux, the majority of cases of acute pyelonephritis in children, documented by DMSA renal scintigraphy, are not associated with VUR* (*55*).

As indicated by the association of certain blood group types with an increased risk for acute pyelonephritis, heredity may play a role in the propensity for developing urinary tract infections. Jantausch et al. found a greater frequency of Lewis antigen negative children in patients hospitalized

Table 3.1
Dysfunctional voiding scoring system

Over the last month	*Almost never*	*Less than half the time*	*About half the time*	*Almost every time*	*Don't know*
1. I have had wet clothes or wet underwear during the day	0	1	2	3	N/A
2. When I wet myself, my underwear is soaked.	0	1	2	3	N/A
3. I miss having a bowel movement every day.	0	1	2	3	N/A
4. I have to push for my bowel movements to come out.	0	1	2	3	N/A
5. I only go to the bathroom one or two times each day.	0	1	2	3	N/A
6. I can hold onto my pee by crossing my legs, squatting or doing the "pee dance."	0	1	2	3	N/A
7. When I have to pee, I cannot wait.	0	1	2	3	N/A
8. I have to push to pee.	0	1	2	3	N/A
9. When I pee it hurts.	0	1	2	3	N/A
10. Parents to answer. Has your child experienced something stressful like the example below? [a]		No (0)		Yes (3)	
Total[b]					

[a]New baby, new home, new school, school problems, abuse (sexual/physical), home problems (divorce/death), special events (birthday), accident/injury, others.

[b]Dysfunctional elimination more likely if score of ≥ 6 in girls or ≥ 9 in boys.

This table was published in Farhat et al. (*52*), 1011–1015. Copyright Elsevier (2000).

for acute urinary tract infections when compared to age-matched controls (*57*). Presumably, Lewis blood group negative individuals are at risk because they lack the secreted antigens, which competitively inhibit binding by pathogenic organisms. Lomberg et al., studying a different phenotypic marker, found that more girls with recurrent non-reflux pyelonephritis had the P-blood group phenotype when compared with healthy controls. In contrast, in a cohort of girls with recurrent pyelonephritis associated with vesicoureteral reflux, the incidence of attaching bacteria and the prevalence of the P-blood group phenotype were not different than in controls. *This would suggest that, in the absence of reflux, P-blood group antigens facilitate infection by bacteria with specific attachment properties. Conversely, the presence of reflux promotes infection with bacteria of lesser pathogenic potential* (*58*).

REFLUX NEPHROPATHY

During the 1970s, "chronic atrophic pyelonephritis" came to be associated with vesicoureteral reflux culminating in acceptance of the term "reflux nephropathy" as synonymous with renal scarring. In studies by Scott and Stansfield (*59*) and Smellie (*60*), between 85 and 100% of kidneys with small, scarred kidneys had VUR. "End-stage" kidneys found during neonatal autopsies were invariably associated with severe vesicoureteral reflux. Consequently, it was suggested that the pathologic changes attributed to reflux might be present in the absence of infection (*61*). Indeed some small children were found to have scars in the absence of a history of urinary tract infection (approximately 13%). Most of these children were infant boys with diffuse renal scarring and severe reflux. Unfortunately, the relationship between vesicoureteral reflux and reflux nephropathy remained clouded for some time. Early experimental animal models which associated sterile intrarenal reflux of urine with renal scarring attributed this to the "water-hammer" effect of VUR on the developing kidney (*62*). However, to promote reflux in these studies, bladder outlet obstruction was created. Ransley and Risdon subsequently challenged this theory using the experimental refluxing porcine model. In contrast to prior studies, bladder outlet obstruction was not created. *Renal parenchymal scarring associated with VUR in the absence of bladder outlet obstruction occurred* only *when infection was present*. Such scarring was typically evident as polar lesions (focal renal scarring) associated with compound calyces. Microscopic evaluation found these calyces to be associated with abnormally shaped papilla, presumably with a greater propensity for intrarenal reflux. In contrast, scarring associated with reflux of sterile urine could only be produced when sustained high pressure was created by obstruction at the bladder neck (*63*). Clinical correlates to this type of sustained high-pressure VUR are few, primarily boys with posterior urethral valves and children with non-compliant bladders associated with neuropathic conditions or severe dysfunctional voiding (Hinman's Syndrome).

In contrast, intermittent high voiding pressure is not sufficient to produce renal scarring in the absence of infection. Smellie et al. also observed that prior urinary tract infection was a requirement for progressive renal scarring in kidneys subtended by refluxing ureters. They did not find evidence of progressive renal scarring in previously normal kidneys that were kept infection-free during follow-up (*64*). *From these studies, one can conclude that the "water-hammer" effect is not a contributor to renal damage in cases of primary VUR*.

Further evidence supporting the primary role that infection plays in the etiology of acquired renal scarring comes from clinical studies. Both clinical and experimental studies have documented acute pyelonephritic damage, often associated with the presence of P-fimbriated *E. coli*, in the absence of demonstrable VUR (*55*). New or progressive scarring is almost always associated with a prior UTI, most often febrile UTI's (*65*–*67*). A clear association between the number of pyelonephritic attacks and the incidence of renal scarring has been reported (*66*, *68*). Renal scarring may be prevented or diminished in some instances by early antibiotic treatment of acute pyelonephritis (*69*–*71*). When VUR is present, new renal scarring is prevented by keeping the patient free of infection with low dose antibiotic prophylaxis (*72*–*74*). Finally, both new and preexistent renal scarring have been reported in children who have febrile UTIs, even in the absence of VUR (*55*).

However, the fact that scarring can occur in the absence of VUR should not discount its importance. The correlation between the severity of VUR and renal scarring is well established (*13*, *64*, *72*, *73*). Furthermore, a recent study reported the risk of scarring affecting >25% of the kidney in children following an episode of DMSA proven acute pyelonephritis was 6% in children without VUR compared to 14% of those with grade I–II VUR and 40% of those with grade III–IV VUR (p=0.0003) (*75*). *This increased risk of scarring associated with more severe VUR is directly attributable to the increased risk of acute pyelonephritis in these patients. Simply stated, recurrent pyelonephritis, not VUR, causes acquired renal scarring*.

Pathogenesis of Post-pyelonephritic Renal Scarring

Experimental studies have helped to elucidate the chain of events involved in post-pyelonephritic renal scarring. Bacterial adherence to uroepithelium elicits an inflammatory cascade proportional to the virulence of the infecting organism. Potent cytokines induce cellular and humoral mediated bacterial killing and chemotaxis of granulocytes. Granulocyte aggregation within capillaries leads to vascular occlusion with resultant renal ischemia (*76*–*78*). Uninvolved areas of the affected kidneys demonstrate normal blood flow when compared with the contralateral normal kidney, as do refluxing kidneys which do not demonstrate evidence of acute pyelonephritis (*79*).

Further ischemia-related alteration to renal tubular epithelium results from the release of superoxide produced, in part, during reperfusion of ischemic tissue (*80*). Superoxide generates oxygen radicals, which are toxic,

not only to the bacteria but also to the surrounding tubular cells (*81*). Other toxic enzymes are also released from lysosomes into the tubular lumen. Renal tubular cell death ensues, thereby propagating the inflammatory reaction into the renal interstitium where further damage occurs. *Ultimately, it is the combination of interstitial damage from both toxic metabolites and renal ischemia that may lead to renal scarring*.

Congenital Reflux Nephropathy

Not all renal scarring is acquired. Severe reflux may be associated with significant renal dysplasia thought to result from abnormal induction of the nephrogenic cord during embryogenesis. In work published with Mackie et al. (*82*) and later Sommer et al. (*83*), F. Douglas Stephens offered an explanation of the relationship between the position of the ectopic ureteral orifice and the degree of renal dysplasia, citing impaired induction of the metanephric blastema by the ureteral bud as causative. The severity of dysplasia depends upon the degree of ectopia of the ureteral bud ranging from small, hypoplastic kidneys with reduced nephron mass to frank dysplasia.

Several reports have described DMSA scan renal functional abnormalities in patients with primary vesicoureteral reflux detected prenatally (*84*–*89*). The reported incidence of renographic abnormalities in these studies has varied widely, ranging from 17–60%. Patients with prenatally detected reflux have been characterized by a greater severity of reflux (72–100% kidneys with ≥grade III VUR) and a preponderance of males (male:female ratio 2:1–5:1). Many of these infants were evaluated by renal scintigraphy prior to any episodes of infection, confirming that the functional abnormalities present at birth represent a congenital fetal nephropathy rather than an acquired abnormality.

One must be cautious in extrapolating findings in these studies to the general population of children with reflux. Infants with reflux detected prenatally represent a select group of patients characterized by male predominance and a high incidence of severe reflux. Urodynamic evaluation has demonstrated hypercontractility with markedly elevated voiding pressures in the majority of these boys, which resolved within 1–2 years (*90*–*92*). Coincident with this, a higher than expected percentage of VUR will resolve in this select group of patients. In contrast, children with reflux detected postnatally are predominantly female, and most have less severe reflux and a history of UTI. *It is clear that not all reflux-associated renal abnormalities are acquired postnatally, and it would appear that both congenital and acquired scarring may occur in the same kidney*. In severe cases of bladder dysfunction, abnormal bladder dynamics may also adversely affect the developing kidney resulting in functional abnormalities.

Sequelae of Renal Scarring/Dysplasia

The most serious long-term sequelae of extensive or progressive scarring is decreased renal function and hypertension. The risk of hypertension in

patients with renal scarring varies, based on length of follow-up and severity of scarring. In follow-up studies of children with renal scarring, as many as 6–13% of children with scarring have developed hypertension (*93–96*). In some cases, it may be associated with progressive renal insufficiency. A long term follow-up study of an older cohort of 294 patients (mean age at presentation 17 months to 3 years) with reflux nephropathy noted that the risk of hypertension increased with age and length of follow-up (*97*). Whereas 8.5% of these patients had hypertension at presentation, 38% were hypertensive at last follow-up (mean age 34.2 years). Hypertension was significantly more common in those with severe bilateral parenchymal scarring. Similarly, in another series 13% (11/83) of children with renal scarring were hypertensive at initial evaluation and another 17% (14/83) developed hypertension over the subsequent 4–20 years (*98*).

Renal Insufficiency

Reflux nephropathy also causes chronic renal insufficiency (CRI) (*90*). It is reported in 5–10% of patients with ESRD presenting for dialysis or renal transplantation and in an even higher percentage of patients under 16 years of age (*99–101*). In one study, the incidence of renal insufficiency in 30 adults who were diagnosed with severe renal scarring as children was 10% (*96*). A follow-up study of an older cohort of 294 patients (mean age at presentation 17.2 years) with reflux nephropathy found that a 2% incidence of renal insufficiency (GFR <40–69 ml/min) at presentation had increased to 24% at last follow-up (mean age 34.2 years). The more extensive the renal scarring, the higher the proportion with renal insufficiency (*97*).

Recent data from the ItalKid Project, a prospective population-based registry started in 1990 documented an incidence of 12.1 cases per million and that renal hypodysplasia associated with primary vesicoureteral reflux alone was responsible for 25.8% of all cases (*102*). The male:female ratio of 3.2:1 and the median age of diagnosis of males was 2 months compared to a median of 9 months for females. In a separate report they noted that the prevalence of males (77.5%), the severity of VUR (grade IV–V) and the early age of diagnosis (18% prenatally) seemed to suggest that congenital renal damage is the major cause of pediatric chronic renal failure in children with VUR (*103*).

Patients demonstrating severe scarring from childhood infections also retain a greater risk for developing UTIs into adulthood. However, not all patients with pyelonephritis in childhood are ill-fated to suffer from hypertension and renal insufficiency later in life. Studies have demonstrated a lack of progression of renal damage in children who are kept infection-free with antimicrobial prophylaxis. Longitudinal studies with long-term follow-up have also clearly demonstrated a decreasing incidence of repeated infections with advancing age. Others have found that despite radiological evidence of renal scarring after an initial childhood UTI, renal function might be well

preserved into adulthood. *Synthesis of these data suggests that the most severe damage from infection occurs early in life. Careful monitoring and prevention of recurrent pyelonephritis will prevent the outcome of infection-related nephropathy in some children. Others, who present with severe congenital nephropathy or after significant scarring has already occurred, will suffer progressive complications. The importance of prevention is underscored by the 12% incidence of "reflux nephropathy" in renal transplant recipients of all ages* (*104*).

DIAGNOSIS OF UTI

Symptoms associated with UTI include irritative complaints (dysuria, frequency, and urgency), suprapubic pain, fever, and malaise. While fever may be the only indicator of a significant urinary tract infection in the non-verbal child, the toilet-trained child may suffer from secondary enuresis and/or other voiding complaints. However, not all children who present with irritative voiding symptoms have UTIs. Conversely, many children have bacteriuria in the absence of fever or urinary symptoms. These observations underscore the importance of documenting urinary infection in children with a urine culture. Although urinalysis is helpful in drawing attention to those who might be infected, the presence or absence of pyuria is not sufficiently reliable for the diagnosis or exclusion of infection. Hoberman et al. compared quantitative urine cultures with an "enhanced" urinalysis for the detection of pyuria and bacilluria in urine specimens obtained *by catheterization* in children presenting with fever. The data obtained demonstrated that UTI is best defined by more than 10 leukocytes/mm^3 on urinalysis combined with urine cultures yielding more than 50,000 CFU/ml (*105*). Dipstick determination for the presence of leukocyte esterase and of nitrite yielded sensitivities of only 52.9 and 31.4%, respectively, in detecting clinically significant bacilluria (greater than 50,000 CFU/ml). In both this and another study of febrile infants, the findings of urinalysis were compared with the results of technetium-99m (Tc-99m) dimercaptosuccinic acid (DMSA) renal scans. Both studies concluded that acute pyelonephritis in febrile infants is almost always associated with the finding of pyuria on urinalysis (*105*, *106*).

In the pre-toilet-trained group, the urine specimen is often initially obtained by applying a collection bag. The results are reliable *only* when the specimen is negative. Contamination is directly related to the length of time the bag is in place. When confirmation of voided urine or immediate treatment is necessary, bladder catheterization or suprapubic aspiration should be employed. In girls and boys who can void on command, midstream specimens are more reliable than bag-collected specimens except in obese children, uncircumcised boys, or girls with significant labial adhesions.

EVALUATION OF UTI

Recommendations for the imaging of children with UTI vary geographically, institutionally, and from one individual to another. However, the rationale for early evaluation of the child with UTI is based on a synthesis of epidemiologic and clinical data. Epidemiological studies have demonstrated a high recurrence rate within 1 year of their first infection in up to 30% of girls and 15% of boys (*12*). Approximately 1/3 of children with culture documented UTIs will have VUR, regardless of symptoms. Clinical parameters have proved unreliable in distinguishing those children with UTIs who also have reflux (*107*). Both experimental studies and clinical observations have shown that significant renal scarring can occur after a single UTI (*1*, *4*, *63*, *108*). Furthermore, the non-specificity of signs and symptoms that typically accompany UTI in infants and toddlers often makes it difficult to determine whether an infection actually represents the first episode (*12*, *109*). In recognizing that recommendations vary, *the policy at Children's National Medical Center is to perform an evaluation after the first culture-documented UTI in all boys and in all girls younger than 5 years of age. Furthermore, all girls with febrile or recurrent infections, particularly those with dysfunctional voiding, should be evaluated regardless of age*. However, it should be acknowledged that prospective data, which prove that early evaluation after the first UTI is necessary or effective in preventing or reducing renal damage, are scarce.

Lower Tract Imaging

The traditional or "bottom up" approach to the evaluation of young children and those with febrile UTIs includes a cystogram to detect the presence of VUR, ureteroceles, posterior urethral valves in boys, or bladder wall trabeculation in children with a history of neuropathic or non-neuropathic voiding dysfunction and a sonogram to evaluate the upper urinary tract. This approach is designed to identify all children with VUR, based on the caveat that all children with VUR need treatment. Standard contrast voiding cystourethrography (VCUG), direct radionuclide cystography (DRC), and indirect radionuclide cystography (IRC) are viable options, each with attendant advantages and disadvantages. A contrast VCUG, with a preliminary plain film radiograph, is usually indicated in boys to exclude obstructive urethral pathology as well as VUR. Although visualization of the urethra in girls is rarely helpful, except in the rare case of a refluxing ectopic ureter, many also prefer contrast cystography as part of the initial evaluation in girls. Contrast cystography not only detects VUR but also provides more anatomical detail (bladder diverticula, duplex collecting systems, ureteroceles) and allows for grading of VUR when present. Some recommend DRC as the initial examination in girls and as follow-up examination in boys and girls with known VUR and after surgery to correct reflux. As DRC also requires catheterization, proponents of its use cite higher sensitivity for the

detection of VUR and a lower radiation doses advantages over standard VCUG. However, newer tailored digital imaging has significantly reduced the amount of radiation exposure from a contrast VCUG (*110*). Sonography enhanced with echogenic sonicated albumin as the "contrast" agent to detect reflux has also been reported for the detection of VUR (*111*). The major advantage of this method is the complete avoidance of radiation. However, this technique still requires catheterization and to date has not gained widespread acceptance.

In contrast to direct cystography, IRC is a means of identifying VUR without urethral catheterization. It relies on rapid and complete renal clearance of an intravenously injected radioisotope. Ideally, images are obtained when the upper urinary tract is cleared of radioisotope, and the tracer is contained in the bladder. The child must therefore be able to voluntarily prolong voiding. An added benefit is the ability to assess upper tract function and drainage. Unfortunately, in a clinical study employing either Tc-99m diethylenetriaminopenta-acetic acid (DTPA) or Tc-99m mercaptoacetyltriglycine (MAG-3) as the radioisotope, vesicoureteral reflux was missed in up to two-thirds of the refluxing ureters, including half of those with VUR grade III or higher. In contrast, false positive studies were rare (*112*).

Regardless of the method employed, some have suggested that cystography be delayed 4–6 weeks following the acute infection to avoid demonstrating transient mild reflux secondary to inflammatory changes of the ureterovesical junction. Others have reported that reflux during infection which disappears shortly after treatment is rare (*113*). However, in a prospective study of 27 children presenting with clinical pyelonephritis, 6 of 21 children with reflux documented on an initial acute phase VCUG did not have reflux demonstrated on a "delayed" VCUG performed 4–6 weeks later (*114*). Thus, a delayed cystogram would have missed the diagnosis of reflux in 28.5% of these children. Since the significance of reflux is greatest during an episode of infection, demonstration of even transient reflux at the time of infection is meaningful. Thus, a prolonged waiting period is not necessary and the cystogram can be performed as soon as the patient is no longer symptomatic and when the urine is sterile. Regardless of the timing of the cystogram, antibiotic prophylaxis is recommended until that time when the cystogram can be safely performed. *With improved imaging techniques and a better understanding of the pathogenesis of UTIs in children, cystoscopy is not routinely indicated in the evaluation of the vast majority of children with urinary tract infection and should be abandoned.*

Upper Tract Imaging

Recommendations for evaluating the upper urinary tract in children presenting with UTI also vary from institution to institution. The ideal study should be painless, safe, cost-effective, and associated with minimal or no radiation, and yet should be capable of detecting all clinically significant

structural malformations as well as renal scarring. Unfortunately, such an all-encompassing study does not exist.

One approach is to initially screen all patients being evaluated for a documented UTI with a renal-bladder sonogram. Sonography is painless, non-invasive, simple to perform, radiation-free, and independent of renal function. It is critical that appropriate images of the ureters, bladder, and true pelvis be obtained routinely to detect the presence of ureteroceles or dilated ureters secondary to ureteral ectopia, ureterovesical junction obstruction, or severe VUR. In children, sonography has been found to be as sensitive as intravenous pyelography for the detection of any significant renal structural abnormality, except for uncomplicated duplication anomalies and renal scarring (*115*, *116*). However, the yield from routine ultrasound evaluation of first time UTIs is low. Recent prospective studies of children with first-time UTIs have reported that less than 1% have clinically significant obstruction, which requires intervention (*117*, *118*). The decreased incidence may be secondary may be secondary to the fact that many of these anomalies are now being detected by prenatal sonography prior to the children experiencing UTI.

Several recent studies have compared the sensitivity of ultrasound with Tc-99m DMSA scans in the detection of both pyelonephritis and renal scarring in children with UTIs. These have demonstrated that the sensitivity of ultrasound in the detection of acute pyelonephritis is one-third that of DMSA renal scans (*119*–*121*) and at best is only 40% in the detection of renal scarring (*122*–*124*). Despite these limitations, *renal and bladder sonography with pre and post void imaging alone is probably sufficient as the initial evaluation in girls with recurrent cystitis and adolescent girls with their first febrile UTI.*

In the absence of reflux, hydronephrosis is best evaluated with diuretic renography using Tc-99m MAG-3. The furosemide-enhanced renal scan combined with computer analysis yields a quantitative assessment of both renal function and drainage of the collecting system. In combination with renal/bladder sonography, one can also accurately define the site of obstruction.

Renal cortical scintigraphy using Tc-99m DMSA has become the gold standard for imaging of renal cortical defects resulting from pyelonephritis. The pathophysiological mechanisms accounting for abnormalities observed on DMSA renal scans during acute infection are probably multifactorial. Renal handling of DMSA relies on tubular cell function and therefore is affected by both renal blood flow and proximal tubular cell function (*125*). Experimental studies in the refluxing piglet model have documented the high accuracy with which DMSA scans can detect areas of reduced renal function associated with histologically proven APN (*125*, *126*). Lesions not detected are microscopic foci of inflammation not evident on gross examination and are not associated with significant parenchymal damage. DMSA has also been shown clearly to have a greater sensitivity and specificity for the

detection of renal cortical scarring when compared with intravenous pyelography, especially in infants and younger children, making this imaging modality ideal for following the progression o f renal parenchymal damage from the time of the initial insult until irreversible scarring occurs (*127–129*). *Renal cortical defects caused by the acute inflammation of pyelonephritis appear as areas of diminished uptake of DMSA with preservation of the renal contour and volume. In contrast, renal scarring is typically demonstrated by focal defects associated with volume loss or contraction of the renal cortex* (*126*, *130*) (Figs. 3.2 and 3.3).

Fig. 3.2. Clinical case. (**a**) Area(s) of photopenia of the renal cortex with preservation of the renal border, the hallmark of acute pyelonephritis on nuclear scintigraphy, in a child without vesicoureteral reflux. (**b**) Resolution of the lesion on follow-up DMSA renal scan.

Since its initial clinical use, numerous prospective studies have documented the findings of DMSA renal scans in children with acute urinary tract infections (*55*). Parenchymal inflammatory damage, documented by DMSA renal scans at the time of infection, has been reported in the majority of patients (50–80%) who present with acute febrile UTI, involving 30–47% of individual renal units. Interestingly, VUR has been shown to be present in only 32–40% of those children with DMSA scan documented acute pyelonephritis. Despite the fact that a majority of patients presenting with fever and clinical findings suspicious for pyelonephritis have abnormalities on DMSA scan, commonly employed clinical and laboratory parameters (fever, elevated ESR and/or CRP, and leukocytosis) are often *unreliable* for the determination of renal parenchymal inflammation (pyelonephritis) (*131–134*). In a recent prospective study, Bergan et al. compared clinical parameters commonly employed for the localization of urinary tract infection with scan findings. Elevated C-reactive protein, ESR, and WBC demonstrated sensitivities of 14, 33, and 23%, respectively, for the detection of renal parenchymal inflammation (*135*).

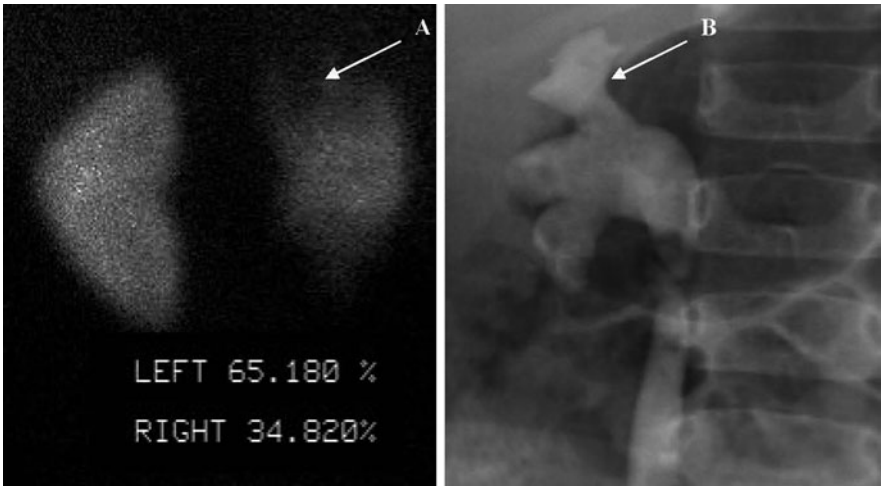

Fig. 3.3. Clinical case. DMSA renal scan demonstrating APN that corresponds exactly to an area consistent with renal scarring on a DMSA renal scan performed 6 months later. While lesions consistent with APN demonstrate photopenia with preservation of the renal contour, renal scars demonstrate loss of volume that disrupts the normal renal contour.

"Top-Down" Approach to Evaluation of UTI

Recently, several studies have advocated the concept of a "top-down" approach to the evaluation of children with UTIs (*136*, *137*). This selective approach focuses on renal status rather than the presence or absence of VUR. *The goal of this approach is to identify only those children with clinically significant VUR, defined as those at risk for renal scarring or recurrent febrile UTIs*. It begins with a DMSA scan, reserving evaluation with a VCUG only for those who have abnormal DMSA findings or subsequent recurrent UTIs. This approach is supported by prior clinical studies that have reported abnormal DMSA findings in 80–90% of children with VUR and febrile UTIs, including almost all with grade III or higher VUR (*55*) (Fig. 3.4). A recent prospective study analyzed this approach in 290 patients (79% with fever ≥38.5°C). DMSA scans performed within 2 weeks of the infection demonstrated abnormalities in 51% of patients, including 26/27 (96%) of those with grade III or higher VUR. Using this approach, the authors conclude that if only those with positive DMSA scans were evaluated with cystography, VCUGs would have been avoided in half of their patients (*138*). *Not only would this reduce the number of children being evaluated with VCUGs, but it would also avoid overtreatment of children with clinically insignificant VUR*.

Regardless of whether one chooses the "bottom-up" or "top-down" approach to the evaluation of UTIs, the use of DMSA in clinical practice is best reserved for those circumstances when it will influence clinical

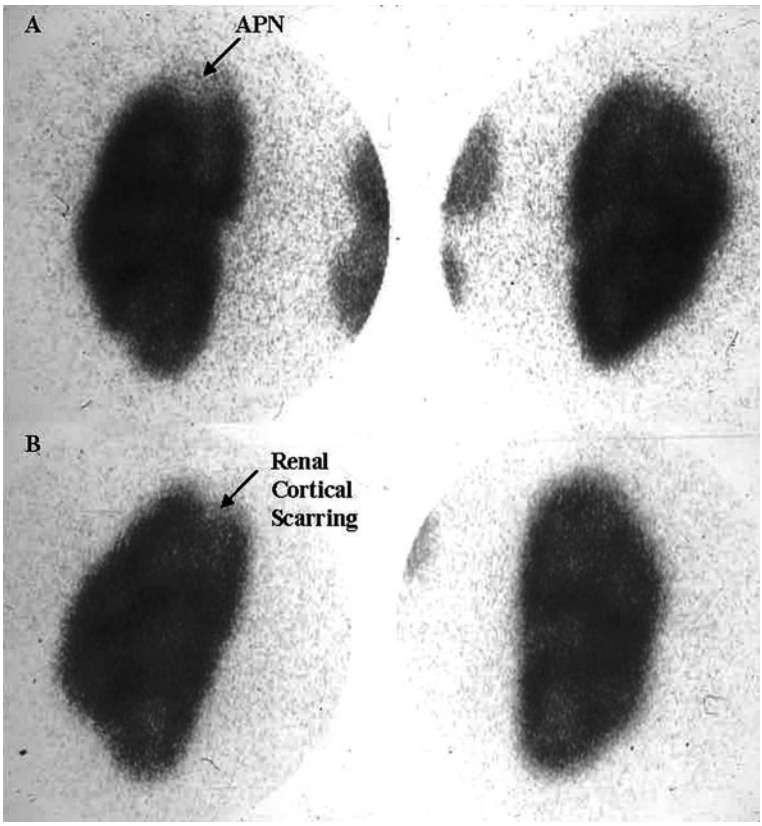

Fig. 3.4. Clinical case. DMSA and VCUG demonstrating acute pyelonephritis on the same side as Grade 3 VUR with evidence of calyceal clubbing, most likely from renal cortical scarring.

management. It is particularly helpful in ascertaining the diagnosis in patients when this is equivocal based on clinical and laboratory findings. For example, neonates and young infants with UTI frequently present with non-specific clinical and laboratory findings. In children with spina bifida, managed by clean intermittent catheterization, chronic bacteriuria is common, thus limiting the diagnostic potential of a positive urine culture when these patients present with fever. Finally DMSA renal scans can detect scarring during the initial presentation of children with VUR, information that may be important for the longitudinal assessment of children managed non-operatively.

TREATMENT OF UTI

The obvious goals of UTI treatment are to provide symptomatic relief and prevent renal damage. *Initial treatment should ideally be based on urine cultures, both for documentation and to provide bacterial antibiotic*

sensitivities. Frequently, therapy is instituted before the results of such cultures become available. Fortunately, because the common uropathogens are susceptible to multiple antibiotics and high urinary levels of these drugs are attainable, high cure rates have still been reported.

Agents that have been used successfully for treatment of acute uncomplicated lower UTIs include sulfonamides, trimethoprim-sulfamethoxazole, nitrofurantoin, trimethoprim, and oral cephalosporins. Ampicillin and amoxicillin, which are used frequently, are two antibiotics to which bacteria are often resistant. Although adjunctive agents have been introduced to circumvent bacterial resistance (sulbactam and clavulonic acid), these add expense and are more often associated with adverse reactions.

Cystitis

The optimal duration of treatment of lower UTIs is controversial. Several studies have advocated short course or even single-dose therapy in children. The obvious advantages of limited regimes are reduced cost, increased compliance, reduced effect on fecal flora, and decreased incidence of side effects. In a meta-analysis of the available data on short course therapy in children, Khan reported that single-dose therapy achieved an overall cure rate of 89%, defined as a negative culture one week after completion of treatment and the lack of recurrence with the same organism. However, the response varied with the agent used. The highest cure rate was obtained with intramuscular aminoglycoside (96%), followed by oral timethoprim-sulfamethoxazole (90%) and amoxicillin (75%). Single-dose therapy was most effective in children with cystitis and in those with an anatomically normal urinary tract (*139*). Madrigal et al. confirmed the immediate effectiveness of single dose therapy, but noted that recurrence rates were higher following therapy in the group receiving single-dose treatment (20.5%) as compared with those receiving antibiotics for three (5.6%) or seven days (8%) (*140*). On the basis of the available data it seems reasonable to treat children with an uncomplicated lower urinary tract infection with a relatively short (3–5 day) course of oral antibiotic. Subsequently, children under the age of 5 years should be maintained on antibiotic prophylaxis until radiologic evaluation has been completed (Table 3.2).

Pyelonephritis

Children with acute pyelonephritis require that more intensive and prolonged treatment be instituted quickly because of evidence suggesting a greater incidence of renal scarring associated with delays in therapy (*6*). *Non-toxic children and infants older than two months can be treated as outpatients as long as compliance is not an issue*. In a prospective randomized clinical trial of 306 children 1–24 months old with febrile UTIs, outpatient treatment with oral 3rd generation cephalosporins was equally effective

Table 3.2
Pediatric dosing of antimicrobials commonly used in the urinary tract

	Route	*Dose (mg/kg/d)*	*Schedule*	*Notes*
Treatment				
Cefazolin	IV	25–50[a]	Q 6–8 h	
Cefepime	IV	100	Q 12 h	
Ceftriaxone	IV, IM	50–75	Q 24 h	
Cefotaxime	IV	50–180[a]	Q 6 h	
Ciprofloxacin	IV	18–30[a]	Q 8 h	
Gentamicin	IV	7.5[a]	Q 24 h	
Amoxicillin	PO	20–40	Q 8 h	
Ampicillin	PO	50–100	Q 6 h	
Cefdinir	PO	7	BID	
Cefprozil	PO	15	BID	
Cefixime	PO	4–8	BID	
Cephalexin	PO	12.5–25	Q 6 h	
Ciprofloxacin	PO	20–40[a]	Q 12 h	
Trimethoprim-Sulfamethoxazole	PO	3–6[a]	BID	
Nitrofurantoin	PO	5–7	Q 6 h	
Prophylaxis				
Amoxicillin	PO		Q HS	For neonates, children >2 months old should receive TMP/SMX or nitrofurantoin
Trimethoprim-Sulfamethoxazole	PO	2	Q HS	Dosing based on trimethoprim component
Nitrofurantoin	PO	2	Q HS	Liquid formulation may cause GI upset, colic, vomiting in which case Macrodantin capsule can be used
Macrodantin Capsule 25 mg (nitrofurantoin)	PO	2	Q HS	<1 year old, contents of ½ capsule added to food >1 year old, contents of 1 capsule added to food

[a]Dose adjustment required with azotemia.

when compared with initial treatment with intravenous antibiotics. There was no difference in treatment success, duration of fever, or subsequent renal scarring on DMSA scans (*141*). *However, it is also reasonable to initiate outpatient therapy with one to two days of a long-acting, third-generation cephalosporin such as ceftriaxone, administered intramuscularly, followed by 10–14 days of an appropriate oral antibiotic*. This approach virtually assures compliance and adequate antimicrobial coverage until the urine culture and sensitivity results are known.

In contrast, toxic children and infants younger than 2 months of age with suspected pyelonephritis should receive immediate intravenous therapy. In these patients, combination therapy including ampicillin and an aminoglycoside is instituted until the urine culture results are known. Alternatively, one of the newer third-generation cephalosporins may be used, but these are more expensive and do not provide comprehensive coverage of gram-positive organisms, including enterococcus. Initially, fluroquinolones were not approved for treatment of childhood UTIs based on concerns regarding adverse joint effects. However, ciprofluroquinolone has since been approved by the FDA for treatment of complicated UTIs in children. Regardless of which antibiotic is chosen, therapy should be continued for 10–14 days, although oral therapy based on the culture sensitivity profile can be substituted in patients older than 1 month of age 48 hours after becoming afebrile.

Asymptomatic Bacteriuria

Treatment of true asymptomatic bacteriuria (ABU) does not appear to be necessary if the urinary tract is otherwise normal (*142*–*144*). The risk for pyelonephritis in infants and young girls with untreated ABU is small, and many demonstrate spontaneous resolution (*12*, *13*). In contrast to infants, treatment of school-age girls with ABU is followed by high recurrence rates up to 80% (*142*). Most are caused by new strains, which carry the risk of being both more resistant and virulent (*145*, *146*). In contrast, when left untreated, spontaneous changes of strain are uncommon (*143*).

Several studies in the 1970s reported that non-treatment of ABU was associated with normal growth of kidneys without the development of renal scarring provided the urinary tract initially appeared normal radiographically (*147*–*150*). In a 4-year follow-up by the Cardiff-Oxford Bacteriuria Study Group in children 5–12 years of age with covert bacteriuria, new or progressive scarring did not occur unless VUR was present (*150*). Similarly, the presence of ABU in the absence of VUR is not a risk factor for renal scarring in children with neuropathic bladders who perform clean intermittent catheterization (*151*).

Hansson et al. compared retrospectively treatment versus non-treatment of ABU in older girls (median age 8 years) with preexistent scarring (*143*). Many also had mild grade I–II VUR. Overall, in girls who received short or long-term antibiotic prophylaxis, 14 patients developed 21 episodes of acute pyelonephritis during a total of 140 patient years of observation. In

contrast, ABU was left untreated in 29 girls for a total of 74 patient years of observation. Only one patient developed acute pyelonephritis.

Based on this information it is reasonable that true ABU, particularly in older girls, be left untreated (*152*). However, in the presence of VUR, the risks of non-treatment of ABU have not been clearly established, particularly in infants and young children. It should also be recognized that voiding dysfunction is commonly found in girls with "asymptomatic bacteriuria," including both detrusor instability and infrequent voiding (*153*). This explains in part the marked tendency for recurrent infection after treatment of ABU with antibiotics alone. Treatment of the underlying voiding dysfunction is key to successful long-term management of these patients.

Antibiotic Prophylaxis

Antibiotic prophylaxis is recommended in children with vesicoureteral reflux (particularly under 8 years of age) and following three documental, symptomatic UTI's in 6 months, or 4 in a year. In children with febrile UTI recurrences, the threshold for starting prophylaxis is lower. Although prophylaxis effectively prevents infection, it cannot be expected to reduce the recurrence rate of urinary infection after therapy has been discontinued. Nevertheless, it is helpful to achieve an infection-free interval in those children with multiple, recurrent urinary infections, many of whom have underlying voiding dysfunction. Attempts to improve voiding dynamics and associated constipation are essential to reducing the recurrence rate of UTIs in these children. Prior to our current understanding of the association of voiding dysfunction and UTIs in children, many of these children were inappropriately managed with urethral dilation and or urethrotomy. These procedures do not affect recurrence rates and should be eliminated from current practice.

The customary doses of antibiotics used as prophylaxis are less than therapeutic doses. The usual practice is to administer one-third to one-half of the therapeutic dose of TMP-SMX or furadantin once or twice daily. Requesting a twice-daily dosing has a pragmatic advantage. If one dose is missed, the child still receives some medication each day. However, in a compliant family, a single night-time dose is usually effective.

It should be noted that the efficacy and necessity of antibiotic prophylaxis has been recently questioned (*154*). Furthermore, there is increasing concern regarding the contribution of antibiotic prophylaxis to the growing emergence of bacterial resistance. Resistance of *E. coli* isolates in the United States is elevated, reaching 36.7, 44.6, and 2.4% for trimethoprim-sulfamethoxazole, ampicllin, and ciprofloxacin, respectively (*155*). Although small randomized controlled trials have reported that antibiotic prophylaxis can be beneficial in high risk groups (*156*, *157*), there is clearly a need for well-designed prospective controlled randomized trials focusing on groups with different risk stratifications.

Renal Abscess

In the past the majority of renal abscesses, a rare form of renal infection, were not caused by ascending infection. Historically, *Staphylococcus aureus* has been the offending agent as a result of hematogenous seeding from a peripheral cutaneous site of origin, or seeding of the contused renal parenchyma after blunt abdominal trauma (*158*, *159*). Diagnosis is often delayed in these patients because urine cultures are negative in most. With the advent of early recognition and effective therapy, the frequency of staphylococcal bacteremia and renal abscesses has decreased. More cases of gram-negative infections in the presence of vesicoureteral reflux or other anatomic abnormalities of the urinary tract are now being seen (*160*).

Most patients with a renal abscess present with high fever, leukocytosis, and an elevated ESR, often accompanied by flank pain. A variety of imaging techniques have been used to diagnose renal abscesses, including IVP and angiography, gallium-67 scintigraphy, sonography, and CT (*161*). The classic treatment of renal abscess has been surgical drainage in addition to appropriate antibiotic therapy. However, improved antibiotics and diagnostic techniques, together with the ability to obtain culture by percutaneous aspiration or drainage under ultrasonic control, have often obviated the neccesity for surgical intervention. In seven patients reported by Schiff et al., 10 days of parenteral antibiotic treatment alone followed by an additional 2 weeks of appropriate oral therapy was successful (*162*). However, in a review of the literature performed by Steele et al., 62% (16/26) of the children with renal abscesses ultimately required drainage (*163*). Unfortunately, no controlled data exist that rigorously compares the resolution rate between children treated with antibiotics alone versus those treated with antibiotics and drainage. Currently, most cases of renal abscess initially can be managed without intervention, percutaneous drainage being reserved for persistent infection. Children who are immunocompromised by virtue of malnutrition or infection with the human immunodeficiency virus are at particular risk for developing recurrent renal abscesses and abscesses containing unusual organisms (*Listeria monocytogenes*) (*164*, *165*). In these circumstances, more aggressive early surgical or percutaneous intervention is often necessary to eradicate the infection.

Xanthogranulomatous Pyelonephritis

Xanthogranulomatous pyelonephritis is an atypical form of severe chronic renal parenchymal infection characterized by unilateral desctruction of parenchyma and accumulation of lipid-laden macrophages (xanthoma cells) either surrounding abscess cavities or as discrete yellow nodules. More than 50 cases of xanthogranulomatous pyelonephritis have been reported in children (*166–168*). The age of presentation has ranged from infancy to 16 years. Most patients present with non-specific symptoms of chronic infection, including weight loss, recurrent fever, failure to thrive, pallor, and

lethargy, although those with the focal form often appear healthy (*166*, *167*). A palpable abdominal mass is present in approximately one-third of cases. Bacterial specimens for culture can be obtained from the urine or renal abscess in the majority of cases, with *Proteus* being the most common organism isolated.

Both diffuse and focal forms of the disease have been reported, with the focal form being more common in children than in adults (*167*). The pathologic and radiologic differences between focal and diffuse xanthogranulomatous pyeloneprhitis have been described (*167*). Radiologic evaluation in the diffuse form of the disease often reveals non-function of the entire kidney. Calcification or stones may be present, although this is less common in the focal form of the disease. Characteristic sonographic or CT appearances of xanthogranulomatous pyelonephritis also have been reported (*169*). However, these features are non-specific and often mimic neoplasia or other forms of chronic inflammatory renal parenchymal disease. Consequently, the correct diagnosis is seldom made preoperatively. Nephrectomy is curative, although partial nephrectomy may be adequate in focal disease, assuming that the diagnosis can be established. No incidence of recurrence in the contralateral kidney has been reported.

Treatment in Renal Failure

The dynamics of antibiotic detoxification and excretion are usually deranged in the child with renal failure. Antibacterial doses need to be adjusted in such patients to avoid adverse reactions. Certain drugs – those that are dependent on renal function for efficacy – are useless in these patients. The frequency of administration of those drugs that are effective in the face of renal failure – rather than their dosages – should be modified based on the degree of renal insufficiency.

CONCLUSIONS

Accurate documentation of UTI in children is essential for proper evaluation and management. Urine cultures with multiple organisms or colony counts less than 50,000–100,000 should be considered suspect and require confirmation, particularly with clean catch specimens. Children with well-documented UTIs should be evaluated based on their age and presenting symptoms. Infants and young children require imaging, usually with a cystogram and ultrasound of the kidneys and bladder. Alternatively, some centers begin with a Tc-99m DMSA scan and use the findings of pyelonephritic changes to determine which children require evaluation with a VCUG. Older girls with febrile UTIs and boys at any age should also be considered for urinary tract imaging. Renal cortical scintigraphy with Tc-99m DMSA has emerged as the imaging study of choice for both acute pyelonephritis and renal scarring in children with UTIs.

Treatment of UTIs in children ideally commences with culture specific antimicrobial therapy, although treatment may be started in the sick child before culture results are available. Short course treatment (3–5 days) is sufficient for children with acute uncomplicated lower urinary tract infections. Children with acute pyelonephritis require 10–14 days of antibiotics, which can be administered on an outpatient basis in older infants and children who are not toxic, as long as compliance is reliable. Patients with first-time UTIs who require imaging should be maintained on low dose antibiotic prophylaxis until their workup is completed. Treatment of asymptomatic bacteriuria does not appear to be necessary if the urinary tract is otherwise normal. Resolution can be anticipated when urinary and bowel habits normalize.

Long-term antibiotic prophylaxis is indicated for children with frequent symptomatic recurrences of UTI and for those with known VUR. Endoscopic and extravesical reimplantation techniques have reduced the morbidity of operative intervention. Diagnosis and treatment of underlying voiding dysfunction and constipation is an essential component of the successful management of UTIs in children.

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REFERENCES

1. Jakobsson B, Berg U, Svensson L: Renal scarring after acute pyelonephritis. Arch Dis Child 70: 111, 1994.
2. Jakobsson B, Nolstadt L, Svensson L, et al: 99mTc-dimercaptosuccinic acid (DMSA) in the diagnosis of acute pyelonephritis in children: relation to clinical and radiological findings. Pediatr Nephrol 6: 328, 1992.
3. Majd M, Rushton HG, Jauntausch B, Weiderman B: Relationship among vesicoureteral reflux, p-fimbriated E. coli, and acute pyelonephritis in children with febrile urinary tract infection. J Pediatr 119: 578, 1991.
4. Rushton HG, Majd M, Jauntausch B, et al: Renal scarring following reflux and non-reflux pyelonephritis in children: evaluation with 99m-tecnetium dimercaptosuccinic acid scintigraphy. J Urol 146: 1327, 1992.
5. Berg UB, Johansson SB: Age as a main determinant of renal functional damage in urinary tract infection. Arch Dis Child 63: 1320, 1988.
6. Smellie JM, Poulton A, Prescod NP: Retrospective study of children with renal scarring associated with reflux and urinary infection. BMJ 308: 1193, 1994.
7. Jacobson SH, et al: Development of hypertension and uremia after pyelonephritis in childhood: 27 year follow-up. BMJ 299: 703, 1989.
8. Bereket G, Fine RN: Etiology of End Stage Renal Disease requiring renal transplant in children between 1987–1993. Pediatric Clinics of North America 42(6): 1603, 1995.
9. Wettergren B, Jodal U, Jonasson G: Epidemiology of bacteriuria in the first year of life. Acta Paediatrica Scandinavia 74: 925, 1985.
10. Savage D, Wilson M, Mchardy M, et al: Bacteriuria in children. Arch Dis Child 48: 8, 1973.

11. McLachlan M, Mellor S, Verrier-Jones E, et al: Urinary tract infection in school girls with covert bacteriuria. Arch Dis Child 50: 253, 1975.
12. Winberg J, Andersen HJ, Bergstrom T, et al: Epidemiology of symptomatic urinary tract infection in childhood. Acta Ped Scand S252: 1–20, 1974.
13. Jodal U, The natural history of bacteriuria in childhood. Infect Dis Clin North Am 1(4): 713, 1987.
14. Bergstrom T, Larson H, Lincoln K, Winberg J: Studies of urinary tract infections in infancy and childhood. J Pediatr 80: 858, 1972.
15. Gillenwater JY, Harrison RB, Kunin CM: Natural history of bacteriuria in school girls: A long-term case-control study. NEJM 301: 396, 1979.
16. Hoberman A, Chao HP, Keller DM, Hickey R, Davis HW, Ellis D: Prevalence of urinary tract infection in febrile infants. J Pediatr 123(1): 17, 1993.
17. Bonadio WA, Smith DS, Sabnis S: The clinical characteristics and infections outcomes of febrile infants aged 8 to 12 weeks. Clin Pediatr (Phila) 33(2): 95, 1994.
18. Siegfried L, Kmetova M, Pazovd H, Molokacova M, Filka J: Virulence associated factors in Escherichia coli strains isolated from children with urinary trtact infections. J Med Microbiol 41(2): 127.
19. Blanco M, Blanco JE, Alonso MP, Blanco J: Virulence factors and O groups of Escherichia coli isolates from patients with acute pyelonephritis, cystitis and asymptomatic bacteruria. Eur J Epidemiology 12(2): 191, 1996.
20. Connell H, de Man P, Jodal U, Lincoln K, Svanborg C: Lack of associated between hemolysin production and acute inflammation in human urinary tract infection. Microb Pathog 14(6): 463, 1993.
21. Winberg J, Bergstrom T, Jacobsson B: Morbidity, age and sex distribution, recurrences and renal scarring in symptomatic urinary tract infection in childhood. Kidney Int 8: S-101, 1975.
22. Ulleryd, Lincoln K, Schultz F, Sandberg T: Virulence characteristics of Escherichia coli in relation to host response in men with symptomatic urinary tract infection. Clin Infect Dis 18(4): 579, 1994.
23. Stamey TA: The role of introital enterobacteria in recurrent urinary tract infections. J Urol 109: 467, 1973.
24. Bollgren I, Winberg J: The periurethral aerobic flora in healthy boys and girls. Acta Ped Scand 65: 81, 1976.
25. Ginsburg CM, McCraken GH: Urinary tract infections in young infants. Pediatr 69: 409, 1982.
26. Svanborg-Eden C, Hanson CA, Jodal U, Lindberg U, Sohl-Akerlund A: Variable adherence to normal human urinary tract epithelial cells of Escherichia coli strains associated with various forms of urinary infection. Lancet 11: 490, 1976.
27. Kallenius G, Mollby R, Svensson SB, Helin I, Hultberg H, Cedergren B, Winberg J: Occurrence of P-fimbriated Escherichia coli in urinary tract infections. Lancet II: 1369, 1981.
28. Jauntausch BA, Wiedermann BL, Hull SI, et al: E. coli virulence factors and 99mTc-dimercaptosuccinic acid renal scan in children with febrile urinary tract infections. Pediatr Infect Dis J 11(5): 343, 1992.
29. Stamey TA, Timothy M., Millar M, et al: Recurrent urinary infections in adult women. The role of introital enterobacteria. Calif Med 115: 1, 1971.
30. Gareau FE, Mackel DC, Boring JR, et al: The acquisition of fecal flora by infants from their mothers during birth. J Pediatr 54: 313, 1959.
31. Patrick MJ: The influence of maternal renal infection on the foetus and infant. Arch Dis Child 42: 208, 1967.
32. Wold AE, Caugant DA, Lidin-Janson G, et al: Resident E. coli strains frequently display uropathogenic characteristics. J Infect Dis 165(1): 46, 1992.
33. Plos K, Connell H, Jodal U, et al: Intestinal carriage of P-fimbriated Escherichia coli and the susceptibility to urinary tract infection in young children. J Infect Dis 171: 625, 1995.

34. Ginsberg C, McCraken, GH: Urinary tract infections in young infants. Pediatr 69: 409, 1982.
35. Bollgren I, Winberg J: The periurethral aerobic bacterial flora in healthy boys and girls. Acta Paediatr Scand 65: 74, 1976.
36. Wiswell TE, Miller GH, Gelston HM: The effect of circumcision status on periurethral bacterial flora during the first year of life. J Pediatr 113: 442, 1988.
37. Rushton HG, Majd M: Pyelonephritis in male infants: How important is the foreskin? J Urol 148: 733, 1992.
38. Koff SA, Murtagh DS: The uninhibited bladder in children: Effect of treatment on recurrence of urinary infection and vesicoureteral reflux. J Urol 130: 1138, 1983.
39. Homsy YL, Nsouli J, Hamberger B, et al: Effects of oxybutinin on vesicoureteral reflux in children. J Urol 134: 1168, 1985.
40. Seruca H: Vesicoureteral reflux and voiding dysfunction: Prospective study. J Urol 142: 494, 1989.
41. Williams MA, Noe HN, Smith RA: The importance of urinary tract infection in the evaluation of the incontinent child. J Urol 151(1): 188, 1994.
42. Herman F: Urinary tract damage in children who wet. Pediatr 54: 143, 1974.
43. Van Gool JD, Kuitjin RH, Donekerwolcke RA, et al: Bladder-sphincter dysfunction, urinary infection and vesicoureteral reflux with special reference to cognitive bladder training. Contrib Nephrol 39: 190, 1984.
44. Snodgrass W: Relationship of voiding dysfunction to urinary tract infection and vesicoureteral reflux in children. Urology 38; 341, 1991.
45. Hjalmas K: Functional daytime incontinence: definitions and epidemiology. Scand J Urol Nephrol 141(sup): 39, 1992.
46. Van Gool JD, Vijverberg MA, de Jong TP: Functional daytime incontinence: Clinical and urodynamic assessment. Scand J Urol Nephrol 141: 58, 1992.
47. Hellstrom A, Hanson E, Hansson S, et al: Association between urinary symptoms at 7 years old and previous urinary tract infection. Arch Dis Child 66: 232, 1991.
48. Hansson S: Urinary incontinence in children and associated problems. Scand J Urol Nephrol 141(sup): 47, 1992.
49. Wan J, Kaplinsky R, Greenfield S: Toilet habits of children evaluated for urinary tract infection. J Urol 154(2 pt 2): 797, 1995.
50. Dohil R, Roberts E, Jones KV, et al: constipation and reversible urinary tract abnormalities. Arch Dis Child 70(1): 56, 1994.
51. Blethyn AJ, Jenkins HR, Roberts R, et al: Radiological evidence of constipation in urinary tract infection. Arch Dis Child 73(6): 534, 1995.
52. Farhat W, Bagli DJ, Capolicchio G, et al: The dysfunctional voiding scoring system: quantitative standardization of dysfunctional voiding symptoms in children. J Urol. 164 (3pt2): 1011, 2000.
53. Upadhyay J, Bolduc S, Bagli DJ, et al: Use of the dysfunctional voiding symptom score to predict resolution of vescoureteral reflux in children with voiding dysfunction. J Urol 169(5): 1842, 2003.
54. Bartkowski DP and Doubrava RG: Ability of a normal voiding dysfunction symptom score to predict uroflowmetry and external urinary sphincter electromyography patterns in children. J Urol 172(5pt1): 1980, 2004.
55. Rushton HG: The evaluation of acute pyelonephritis and renal scarring with technetium 99m-dimercaptosuccinic acid renal scintigraphy: evolving concepts and future directions. Pediatr Nephrol 11: 108, 1997.
56. Lomberg H, Hellstrom M, Jodal U: Virulence associated traits in Escherichia coli causing first and recurrent episodes of urinary tract infection in children with or without reflux. J Infect Dis 150: 561, 1984.
57. Jauntausch BA, Criss VR, O'Donnell R, et al: Association of Lewis blood group phenotypes with urinary infection in children. J Pediatr 124(6): 863, 1994.
58. Lomberg H, Hanson LA, Jacobsson B, et al: correlation of P blood group, vesicoureteral reflux, and bacterial attachment in patients with recurrent pyelonephritis. N Engl J Med 308: 1189, 1983.

59. Scott JES, Stansfield JM: Ureteric reflux and kidney scarring in children. Arch Dis Child 43: 468, 1968.
60. Smellie JM, Normand ICS; Experience of follow-up of children with urinary tract infection. In Urinary Tract Infection, O'Grady and Brumfitt ed, London, Oxford University Press, 1988, pp 123–135.
61. Bailey RR, The relationship of vesico-ureteric reflux to urinary tract infection and chronic pyelonephritis-reflux nephropathy. Clin Nephrol 1:132, 1973.
62. Hodson et al: Kidney Int 8: S-50, 1975.
63. Ransley PG, Risdon RA: Reflex and renal scarring. Br J Radol [Sup] 14: 1, 1978.
64. Smellie J, Edwards D, Hunter N, et al: Vesicoureteral reflux and renal scarring. Kidney Int 8(Sup) 65, 1975.
65. Smellie JM, Ransley PG, Normand ICS, et al: Development of new renal scars: a collaborative study. Br Med J 290:1957, 1985.
66. Winberg J, Bollgren I, Kallenius G, Mollby R, Svenson SB: Clinical pyelonephritis and focal renal scarring: a selected review of pathogenesis, prevention and prognosis. Pediatr Clin North Am 22:801, 1982.
67. Huland H, Busch R: Pyelonephritic scarring in 213 patients with upper and lower tract infections: Long-term follow-up. J Urol 132:146, 1984
68. Goldraich NP, Goldraich IH, Anselmi OE, et al: Reflux nephropathy: the clinical picture in South Brazilian children. Contrib Nephrol 39:52, 1984.
69. Glauser MP, Lyons JM, Braude AI: Prevention of chronic experimental pyelonephritis by suppression of acute suppuration. J Clin Invest 61: 403, 1978.
70. Ransley PG, Risdon RA: Reflux nephropathy: effects of antimicrobial therapy on the evolution of the early pyelonephritic scar. Kidney Int 20: 733, 1981.
71. Doganis D, Siafas K, Mavrikou M, et al: Does early treatment of urinary tract infection prevent renal damage. Pediatrics online Sept 2007, www.pediatrics.org/cgi/content/full/peds.2006–2417vl.
72. Skoog SJ, Belman AB, Majd M: A nonsurgical approach to the management of primary vesicoureteral reflux. J Urol 138: 941, 1987.
73. Bellinger MF, Duckett JW: Vesicoureteral reflux: a comparison of non-surgical and surgical management. Contrib Nephrol 39: 133, 1984.
74. Edwards D, Normand ICS, Prescod N, Smellie JM: Disappearance of vesicoureteric reflux during long-term antibiotic prophylaxis of urinary tract infection. Br Med J 2:285, 1977.
75. Gonzalez E, Papazyan J-P, Girardin E: Impact of vesicoureteral reflux on the size of renal lesions after an episode of acute pyelonephritis. J Urol 173: 571, 2005.
76. Kaack MB, Dowling KJ, Patterson GM, and Roberts JA: Immunology of pyelonephritis: E. coli causes granulocytic aggregation and renal ischemia. J Urol: 136: 1117, 1986.
77. Hill GS, Clarck RL: A comparative angiographic, microangiographic, and histologic study of experimental pyelonephritis. Invest Radiol 7: 33, 1972.
78. Androulakakis PA, Ransley, PG, Risdon RA, et al: Microvascular changes in the early stage of reflux pyelonephritis: An experimental study in the pig kidney. Eur Urol 13: 219, 1987.
79. Majd M, Rushton HG: Renal cortical scintigraphy in the diagnosis of acute pyelonephritis. Semin Nucl Med 22: 98, 1992.
80. McCord, JM: Oxygen-derived free radicals in post ischemic tissue injury. N Eng J Med 312: 159, 1985.
81. Roberts JA, Ruth JK, Dominique GL, et al: Immunology of pyelonephritis in the primate model: Effect of superoxide dismutase. J Urol 128: 1394, 1982.
82. Mackie GG, Stephens FD: Duplex kidneys: a correlation of renal dysplasia with position of the ureteral orifice. J Urol 114: 2743, 1975.
83. Sommer JT, Stephens FD: Morphogenesis of nephropathy with partial ureteral obstruction and vesicoureteral reflux. J Urol 125: 67, 1981.
84. Gordon AC, Thomas DFM, Arthur AJ, et al: Prenatally diagnosed reflux: A follow-up study. Br J Urol 65: 407, 1990.

85. Najmaldin A, Burge DM, Atwell TD: Reflux nephropathy secondary to intrauterine vesicoureteric reflux. J Ped Surg 25: 387, 1990.
86. Anderson PAM, Rickwood AMK: features of primary vesicoureteric reflux detected by prenatal sonography. Br J Urol 67: 267, 1991.
87. Sheridan M, Jewkes F, Gough DCS: Reflux nephropathy in the 1st year of life-the role of infection. Pediatr Surg Int 6: 214, 1991.
88. Crabbe DCG, Thomas DFM, Gordon AC, et al: Use of 99mtechnetium-dimercaptosuccinic acid to study patterns of renal damage associated with prenatally detected vesicouretral reflux. J Urol 148: 1229, 1992.
89. Burge DM, Griffiths MD, Malone PS, et al: Fetal vesicoureteral reflux: Outcome following conservative postnatal management. J Urol 148: 1743, 1992.
90. Sillen U, Hjalmas K, Aili M, et al: Pronounced detrusor hypercontractility in infants with gross bilateral reflux. J Urol 148:598, 1992.
91. Sillen U, Bachelard M, Hermanson G, et al: Gross bilateral reflux in infants: gradual decrease of initial detrusor hypercontrractility. J Urol 155: 668, 1996.
92. Chandra M, Maddix H, McVicar M: Transient urodynamic dysfunction of infancy: relationship to urinary tract infections and vesicoureteral reflux. J Urol 155: 673–677, 1996.
93. Wallace DMA, Rothwell DL, Wiiliams DI, et al: The long-term follow-up of surgically treated vesicoureteric reflux. Br J Urol 50: 479, 1978.
94. Heale WF: hypertension and reflux nephropathy. Aust Paediatr J 13: 56, 1977.
95. Goonasekera CD, Shah V, Wade AM, et al: 15 –year follow-up of renin and blood pressure in reflux nephropathy. Lancet 347: 640, 1996.
96. Martinell J, Lidin-Janson G, Jagenburg R, et al: Girls prone to urinary infections followed into adulthood. Indices of disease. Pediatr Nephrol 10: 139, 1996.
97. Jacobson SH, Eklof O, Eriksson CG, et al: Development of hypertension and uraemia after pyelonephritis in childhood; twenty-seven year follow-up. Br Med J 299: 703, 1989.
98. Zhang Y, Bailey RR: A long term follow-up of adults with reflux nephropathy. New Zealand Med J 108: 142, 1995.
99. Salvatierra O, Tanagho EA: Reflux as a cause of end stage kidney disease: report of 32 cases. J Urol 117:441, 1977.
100. Disney APS: Reflux nephropathy in Australia and New Zealand: Prevalence, incidence and management – 1975–1989. In: Bailey RR, ed. Second CJ Hodson Symposium on Reflux Nephropathy. Christ Church, New Zealand: Design Printing Services, 1991: 53–56, 1991.
101. Bailey RR, Lynn KL, Robson RA: End-Stage Reflux Nephropathy. Renal Failure 16:27, 1994.
102. Ardissino G, Dacco V, testa S, et al: Epidemiology of chronic renal failure in children: data from the ItalKid Project. Pediatrics 111(4 Pt 1): e382, 2003.
103. Marra G, Oppezzo C, Ardissino G, et al: Severe vesicoureteral reflux and chronic renal failure: a condition peculiar to male gender? Data from the ItalKid Project. J Pediatr 144: 677, 2004.
104. UNOS Transplant Data 1996.
105. Hoberman A, Wold ER, Reynolds EA, et al: Pyuria and bacteriuria in urine specimens obtained by catheter from young children with fever. J Pediatr 124(4): 513, 1994.
106. Landau D, Turner ME, Brennan J, and Majd M: The value of urinalysis in differentiating acute pyelonephritis from lower urinary tract infection in febrile infants. Pediatr Infect Dis J 13: 777, 1994.
107. Smellie JM, Normad ICS, Katz G: Children with urinary infection: A comparison of those with and without vesicoureteric reflux. Kidney Int 20: 717, 1981.
108. Risdon RA, Godley MC, Gordon I, Ransley PG: Renal pathology and 99m Tc-DMSA image before and after treatment of the evolving pyelonephritic scar: an experimental study. J Urol 152: 1260, 1994.
109. Busch R, Huland H: Correlation of symptoms and results of direct bacterial localization in patients with urinary tract infection. J Urol 132: 282, 1984.

110. Kleinman PK, Diamond DA, Karellas A, et al: Tailored low-dose fluoroscopic voiding cystourethrography for the re-evaluation of vesicoureteral reflux in girls. AJR 162: 1151, 1994.
111. Atala A, Wible H, Share JC, et al: Sonography with sonicated albumin in detection of vesicoureteral reflux. J Urol 150: 756, 1993.
112. Sadeleer CD, Boe VD, Kenppens F, et al: How good is technetium-99m mercaptoacetyltriglycine indirect cystography? Eur J Nuc Med 21: 23, 1994.
113. Gross GW, Lebowitz RL, Infection does not cause reflux. AJR 137: 929, 1981.
114. Hanna MK: Occult vesicoureteral reflux. In Dialogues in Pediatric Urology vol 20(1), Miller WJ ed, William J: Miller Associates, Inc, New York, 1997.
115. Kangarloo H, Gold RH, Fine RN, et al: Urinary infection in infants and children evaluated by ultrasound. Radiology 154: 367, 1985.
116. Jequier S, Forbes PA, Negrady MB: The value of ultrasound as a screening procedure in first documented urinary tract infections in children. J Ultrasound Med 4: 393, 1985.
117. Hoberman A, Charron M, Hickey RW, et al: N Engl J Med 16: 348(3):195, 2003.
118. Mucci B, Maguire B: Does routine ultrasound have a role in the investigation of children with urinary tract infection? Clin Radiol 49(5): 324, 1994.
119. Bjorgvinsson E, Majd M, Eggli DK: Diagnosis of acute pyelonephritis in children: comparison of sonography and 99m-Tc DMSA scintigraphy. AJR 157: 539, 1991.
120. MacKenzie JR, Fowler K, Hollman AS, et al: The value of ultrasound in acute urinary tract infection. Br J Urol 74(2): 240, 1994.
121. Sty JR, Wells RG, Starshak RJ, et al: Imaging in acute renal infection in children. AJR 148: 471, 1987.
122. Rickwood AM, Canty HM, McKendrick T, et al: Current imaging of childhood urinary infections: prospective survey. BMJ 304(6828): 663, 1992.
123. Tasker AD, Lindsell DR, Moncrieff M: Can ultrasound reliably detect renal scarring in children with urinary tract infection? Clin Radiol 47(3): 177, 1993.
124. Morothy I, Wheat D, Gordon I: Ultrasonography in the evaluation of renal scarring using DMSA scan as the gold standard. Pediatr Nephrol 19(2): 153, 2004.
125. Parkhouse HF, Godley ML, Cooper J, et al: Renal imaging with 99m-Tc-labelled DMSA in the detection of acute pyelonephritis: an experimental study in the pig. Nuc Med Commun 10: 63, 1989.
126. Rushton HG, Majd M, Chandra R, Yim D: Evaluation of 99m-Technetium-dimercaptosuccinic acid renal scans in experimental acute pyelonephritis in piglets. J Urol (part 2) 140: 1169, 1988.
127. Merrick MV, Uttley WS, Wild SR: The detection of pyelonephritic scarring in children by radioisotope imaging. Br J Radiol 53: 544, 1980.
128. Goldraich NP, Ramos DL, Goldraich JH: Urography versus DMSA scan in children with vesicoureteral reflux. Pediatr Nephrol 3: 1, 1987.
129. Elison BS, Taylor D, Van Der Wall H, et al: Comparison of DMSA scintigraphy with intravenous urography for the detection of renal scarring and its correlation with vesicoureteral reflux. J Urol 69: 294, 1992.
130. Risdon RA, Godley ML, Parkhouse HF, et al: Renal pathology in the 99m-Tc-DMSA image during the evolution of the early pyelonephritic scar: an experimental study. J Urol 151: 767, 1994.
131. Benador D, Benador N, Slosman DO, et al: Cortical scintigraphy in the evaluation of renal parenchymal changes in children with pyelonephritis. J Pediatr 124: 17, 1994.
132. Melis K, Vandevivere J, Hoskens C, et al: Involvement of the renal parenchyma in acute urinary tract infection: the contribution of 99mTc dimercaptosuccinic acid. Eur J Pediatr 151(7): 536, 1992.
133. Stokland E, Hellstrom M, Jacobsson B, et al: Early 99mTc-dimercaptosuccinic acid scintigraphy in symptomatic first time urinary tract infection. Acta Pediatr 85(4): 430, 1996.
134. Stokland E, Hellstrom M, Jacobsson B, et al: Renal damage one year after first urinary tract infection: role of dimercaptosuccinic acid scintigraphy. J Pediatr 129(6): 815, 1996.

135. Bergan N, Bircan ZE, Hasanoghu E, et al: The importance of 99m-Tc DMSA scanning in the localization of childhood urinary tract infections. Int Urol Nephrol 25(1): 11, 1993.
136. Tseng MH, Lin WJ, Lo WT: Does a normal DMSA obviate the performance of voiding cystourethrography in evaluation of young children after their first urinary tract infection. J Pediatr 150(1): 96, 2007.
137. Hansson S, Dhamey M, Sigstrom O: Dimercaptosuccinic acid scintigraphy instead of voiding cystourethrography for infants with urinary tract infection. J Urol 172: 1071, 2004.
138. Preda I, Jodal U, Sixt R, et al: Normal DMSA scintigraphy makes voiding cystourethrography unnecessary in the evaluation after urinary tract infection. J Pediatr (Online Aug 8, 2007, press pending).
139. Khan AJ: Efficacy of single-dose therapy of urinary tract infection in infants and children: A review. J Natl Med Assoc 86:690, 1994.
140. Madrigal G, Odoi CM, Mohs E, et al: Single-dose antibiotic therapy is not as effective as conventional regimens for management of acute urinary tract infections in children. Pediatr Infect Dis J 7:316, 1988.
141. Hoberman A, Walkd ER, Hickey RW, et al: Oral versus initial intravenous therapy for urinary tract infections in young febrile children. Pediatrics 104(1 Pt 1): 79, 1999.
142. Eichenwald HF: Some aspects of the diagnosis and management of urinary tract infection in children and adolscents. Pediat Infect Dis J 5: 760, 1986.
143. Hansson S, Caugant D, Jodal U, Svanborg-Eden C: Untreated asymptomatic bacteriuria in girls: I. – Stability of urinary isolates. Br Med J 298: 853–855, 1989.
144. White RHR: Management of urinary tract infection. Arch Dis Child 62: 421, 1987.
145. Bergstrom T, Lincoln K, Orskov F, et al: Studies of urinary tract infections in infancy and children. VIII Reinfection vs relapse in recurrent urinary tract infections: Evaluation by means of identification of infecting organisms. J Pediatr 72: 13, 1967.
146. McGeachie J: Recurrent infection of the urinary tract: reinfection or recrudescence? Br Med J 1: 952, 1966.
147. Newcastle Covert Bacteriuria Research Group: Covert bacteriuria in schoolgirls in Newcastle upon Tyne. A 5-year follow-up. Arch Dis Child 56: 585, 1981.
148. Savage DCL, Howie G, Adler K, Wilson MI: Controlled trial of therapy in covert bacteriuria in childhood. Lancet 1: 358–361, 1975.
149. Lindberg U, Claesson I, Hanson LA et al: Asymptomatic bacteriuria in schoolgirls: VIII. Clinical course during a three-year follow-up. J Pediatr 92: 194, 1978.
150. Cardiff-Oxford Bacteriuria Study Group: Sequelae of covert bacteriuria in school children. Lancet 1: 889, 1978.
151. Ottolini MC, Scher CM, Rushton HG, et al: Relationship of asymptomatic bacteriuria and renal scarring in children with neuropathic bladders who are practicing clean intermittent catheterization. J Pediatr 127(3): 368, 1995.
152. Linshaw M: Asymptomatic bacteriuria and vesicoureteral reflux in children. Kid Inter 50: 312, 1996.
153. Hansson S, Hjalmas K, Jodal U: Lower urinary tract dysfunction in girls with asymptomatic or covert bacteriuria. J Urol 143: 333, 1990.
154. Williams G, Lee A, Craig JC: Antibiotics for the prevention of urinary tract infection in children: a systematic review of randomized controlled trials. J Pediatr 138: 868, 2001.
155. Gaspari RJ, Dickson E, Karlowsky J, et al: Antibiotic resistance trends in paediatric uropathogens. Int J Anitmicrob Agents 26(4): 267, 2005.
156. Lohr JA, Nunley DH, et al: Prevention of recurrent urinary tract infections in girls. Pediatrics 59: 562, 1977.
157. Smellie JM, Gruneberg RN, Normand ICS, et al: Trimethoprim-sulfamethoxazole and trimethoprim alone in the prophylaxis of childhood urinary tract infection. Rev Infect Dis 4: 461, 1982.
158. Rote AR, Bauer SB, Retik AB: Renal abscess in children. J Urol 119: 254, 1978.
159. Vachvanichsanong P, Dissaneewate P, Patrapinyokul S, Pripatananont C, Sujijantararat P: Renal abscess in healthy children: report of three cases. Pediatr Nephrol 6(3): 273–275, 1992.

160. Timmons JW, Perlmutter AD: Renal abscess: a changing concept. J Urol 115: 299, 1976.
161. Wippermann CF, Schofer O, Beetz R, Schumacher R, Riedmeller H, Buttner J: Renal abscesses in childhood: diagnostic and therapeutic progress. Pediatr Infect Dis J 10(6): 446–450, 1991.
162. Schiff Jr. M, Glickman M, Weiss RM eal: Antibiotic treatment of renal carbuncle. Ann Intern Med 8: 305, 1977.
163. Steele BT, Petrou C, de Maria J: Renal abscesses in children. Urology 36(4): 325–328, 1990.
164. Brandeis JM, Baskin LS, Kogan BA, Wara D, Corenbaum A: Recurrent Staphylococcus aureus renal abscess in a child positive for the human immunodeficiency virus. Urology 46(2): 246–248, 1995.
165. Gomber S, Revathi G, Krishna A, Gupta A: Perinephric abscess (presenting as abdominal pain) due to Listeria monocytogenes. Ann Trop Paediatr 18(1): 61–62, 1998.
166. Yazaki T, Ishikawa S, Ogawa Y et al: Xanthogranulomatous pyelonephritis in childhood: case report and review of english and Japanese literature. J Urology 127(1): 80–83, 1982.
167. Watson AR, Marsden HB, Cendron Meal: Renal pseudotumors caused by xanthogranulomatous pyelonephritis. Arch Dis Child 57: 635, 1982.
168. Goodman TR, McHugh K, Lindsell DR: Paediatric xanthogranulomatous pyelonephritis. Int J Clin Pract 52(1): 43–45, 1998.
169. Subramanyam BR, Megibow AJ, Raghavendra BNea: Diffuse xanthogranulomatous pyelonephritis: analysis by compouted toomography and sonography. Urol Radiol 4: 5, 1982.

4 Voiding Dysfunction, Urinary Incontinence, and Urodynamics

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Abstract Voiding dysfunction in children is a common problem constituting nearly 40% of patient visits to a pediatric urologist. Although most of these children present with incontinence either daytime, or nocturnal, or both, some present with recurrent urinary tract infection, hematuria, and pain. Voiding dysfunction could be an isolated problem or in other cases form part of a wider neurological disorder. In this chapter we discuss non-neurological voiding dysfunction in children. We describe the ICCS classification of voiding dysfunction, which forms the backbone for the present day work up for these children. The common presenting symptoms, appropriate work up, diagnosis, and management of these children are discussed in detail.

Keywords Incontinence · Enuresis · Children · Urodynamics · Biofeedback

INTRODUCTION

Voiding dysfunction in children is a common problem constituting nearly 40% of patient visits to a pediatric urologist. Although most of these children present with incontinence, daytime and/or nocturnal, some present with recurrent urinary tract infection, hematuria, and pain. Voiding dysfunction could be an isolated problem or in other cases form part of a wider neurological disorder. In this chapter we discuss non-neurological voiding dysfunction in children. We describe the ICCS classification of voiding dysfunction which forms the backbone for the present day work up for these children. The common presenting symptoms, appropriate work up, diagnosis, and management of these children are discussed in detail.

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BACKGROUND AND EPIDEMIOLOGY

Disorders of voiding in children pose considerable challenges for the child, the parents, and the physicians caring for them. It is important that a thorough history, directed physical examination, proper use of imaging, and proper employment of urodynamics studies be combined to best establish the etiology of the child's complaints. This approach should allow urologists to apply a management plan targeted at treating the underlying causes. In this chapter, we discuss voiding dysfunction, enuresis, and urodynamics so that the general urologist can apply the principles listed above to best effect a positive outcome on voiding dysfunction in children.

There has been considerable progress in the area of pediatric voiding dysfunction. Previously, lower urinary tract dysfunction was interchangeably called dysfunctional voiding, overactive bladder, incontinence, and voiding dysfunction among other labels resulting in inconsistency in the literature. To mitigate against this confusion and establish consistency, the International Children's Continence Society (ICCS), a multinational and multidisciplinary organization, established definitions for various voiding symptoms (*1*). "Voiding Dysfunction" is the recommended term for various functional lower urinary tract symptoms in children without a neurogenic or anatomic abnormality. Voiding dysfunction may constitute up to 40% of pediatric urology visits (*2*) as it affects 15% of 6-year-old children (*3*). Incontinence, both daytime and nocturnal, raises important psychosocial concerns in school-aged children. High-pressure voiding may cause pain and may lead to long-term detriment of kidney function from recurrent urinary tract infections and vesicoureteral reflux (*4*). Hence, it is essential to correctly diagnose and treat these patients appropriately.

Nocturnal enuresis affects 5–7 million (*5*) American children. Since 20% of children with nocturnal enuresis also have daytime symptoms, the ICCS sought to abrogate confusion in nomenclature. Accordingly, nocturnal enuresis may be divided into monosymptomatic (isolated nocturnal enuresis), non-monosymptomatic or complicated (associated with other symptoms like frequency, urgency, and daytime symptoms), primary (never been dry at night time), which accounts for 80% of all patients, and secondary (previously has been dry at night).

PATHOPHYSIOLOGY

There have been several advances in the understanding of the development of bladder control. Classically, voiding in newborn children is a reflex phenomenon initiated by the activation of bladder stretch receptors upon filling leading to potentially 20 voids per day. However, recent evidence indicates the influence of some degree of cortical input (*6*). The child then matures by developing sensory appreciation of bladder filling and then progressing to motor control with initiation of bladder contraction

and eventually to sphincter control and continence. Continence leads to an increased bladder capacity and decreased frequency of voiding.

Daytime continence is achieved first. Brazelton (*7*) found 26% of children achieved daytime continence by 2 years, 85% by 30 months, and 98% by 3 years. Jansson (*8*) followed children from birth to 6 years with regular visits assessing continence and voiding patterns; the median age of daytime continence was 3.5 years and night time continence was 4 years without gender differences. At age 5 years, approximately 20% of children will bed-wet at least monthly. The incidence decreases to roughly 10% by age 6 years and only 1–2% at 15 years. The condition spontaneously resolves at the rate of 15% per year after age 6 years. Gender influences the incidence as 90% of nightly bed-wetters are male children (*9*).

ETIOLOGY OF NOCTURNAL ENURESIS

The exact cause of nocturnal enuresis is felt to be multifactorial. Some of these factors include maturational delay of bladder development, genetic factors, endocrine dysfunction, sleep disorders, and psychological issues.

Genetic factors: A positive family history is noted among 65–85% of enuretic children with a positive paternal side being more significant than from the maternal side (RR 7.1 vs 5.2) (*10*). Norgaard reported a 77% risk of enuresis to the child born of two enuretic parents compared to 43% when one parent had a positive history and 15% when neither parent was enuretic (*11*). Concordance is higher in monozygotic twins compared to dizygotic twins (68% vs 36%) (*12*). An autosomal dominant form with 90% penetrance has been identified in some Danish families in the chromosome 13 (*13*).

Bladder capacity and function: Functional bladder capacity and detrusor instability have been controversial causes of nocturnal enuresis. Urodynamic (UDS) testing revealed identifiable abnormalities in 15% of enuretic children compared to 90% of children with diurnal enuresis (*14*). When compared with non-enuretic children, enuretics have lower voided volumes (*15*). However, recent evidence suggests that enuretic children do not have any urodynamic parameters that are consistently different from their continent counterparts (*16*, *17*). But the above studies did reveal increased detrusor contractions and decreased pelvic floor activity during enuretic episodes.

Nocturnal Polyuria and ADH: ADH has a natural circadian rhythm with night time increases. It has been postulated that enuretic children have a decrease in ADH secretion or responsiveness to circulating ADH leading to increased urine production and accelerated bladder filling and incontinence. Some studies demonstrate lower ADH levels in enuretic children compared to non-enuretic children (*18*) while other studies do not (*19*). Similarly, enuretic and non-enuretic children have been found to have comparable urinary osmolalities (*20*). Hence, ADH's role in nocturnal enuresis is controversial.

Psychological and sleep disorders: Sleep studies suggest that enuretic children are deep sleepers and fail more attempts of arousal compared to age-matched controls (*21*). EEG studies on enuretic children show characteristic findings that progressively mature to normal as the child matures to have a continent bladder function (*22*).

Psychological factors, once considered as the primary etiology of primary nocturnal enuresis, are now controversial at most. Psychological issues may arise as a result of enuresis rather than causing it. Attention deficit hyperactivity disorder has been associated with nocturnal enuresis (*23*) but it is unclear whether it is the cause or effect of enuresis. In contrast, secondary nocturnal enuresis has been associated with behavioral and psychological issues such as parental divorce or sibling rivalry.

ICCS DEFINITIONS OF VOIDING SYMPTOMS

To maintain standardization of terminology and facilitate communication, the ICCS developed definitions of various voiding dysfunction symptoms and categories (*1*).

Daytime frequency – Children >5 years are observed to void between 3–7 times daily. Increased frequency is defined as >8 voids daily and decreased frequency as < 3 voids.

Urgency – Used only in children >5 years or after attainment of bladder control. Urgency is defined as a sudden and unexpected experience of an immediate need to void.

Nocturia – Children >5 years awakening to void at night.

Hesitancy – Children >5 years or any age after achieving bladder control with difficulty initiating a void.

Straining – Relevant in all age groups; defined as external pressure applied on the abdominal wall to initiate and maintain voiding.

Weak stream – Relevant in all age groups; observed ejection of urine with weak force.

Intermittency – When voiding occurs in discrete spurts instead of a continuous stream. It is considered physiological up to 3 years if not associated with straining.

Other symptoms – Some other symptoms in children with voiding dysfunction include the following:

- Holding maneuvers like standing tiptoe, forcibly crossing legs, or squatting with heel pressed to perineum (Vincent's curtsy). Relevant in children >5 years.
- Feeling of incomplete emptying.
- Post-micturition dribble. The involuntary leakage of urine immediately after voiding. Relevant in children >5 years.
- Genital and lower urinary tract pain. Mostly non-specific and difficult to localize.

ICCS CLASSIFICATION OF INCONTINENCE

Incontinence, defined as an uncontrollable leakage of urine, is stratified into two broad categories: continuous and intermittent. Continuous is constant urine leakage seen in congenital anomalies like ectopic ureters. Intermittent incontinence is seen in functional voiding dysfunction and will be discussed in more detail. Discrete amounts of urine leakage can occur during the day or during sleep. Daytime incontinence is intermittent incontinence during daytime. Nocturnal incontinence is synonymous with enuresis or nocturnal enuresis and is defined as intermittent incontinence while asleep. ICCS classification goes on to define the underlying abnormalities of bladder function resulting in daytime incontinence, which are discussed below.

INCONTINENCE

Daytime incontinence is defined as a wetting accident once every 2 weeks in children more than 5 years. In a population based survey of over 1400 primary school children, the incidence of daytime incontinence was 19.2% and was related to emotional stress, positive paternal family history, or male sibling history of daytime incontinence by multivariate analysis (*24*). The incidence is inversely related to age as it is seen in 10% of 5–6 year olds decreasing to 4% of 12- to 18–year-old children (*25*). The following bladder functional abnormalities are recognized by the ICCS as related to daytime incontinence.

Overactive bladder/Urge incontinence: Overactive bladder (OAB) is the second most common voiding dysfunction in children (*26*) and is defined as abnormal detrusor overactivity in the filling phase of a cystometric evaluation. Urgency is the subjective hallmark of OAB and helps secure the clinical diagnosis. Involuntary uncontrolled bladder contractions result in sudden urgency with the child performing holding maneuvers like Vincent's curtsy (*27*) leading to high voiding pressure and post void residuals. A Swedish group reported that at 7 years of age 21% of girls and 18% of boys had moderate to severe urgency (*28*) and symptoms improved with age; the incidence was 6% in girls and 1% in boys at 17 years (*29*).

Voiding postponement: Children, particularly those with behavioral or psychological comorbidities, were noted to postpone micturition often in specific situations using holding maneuvers. This results in decreased frequency and a constant feeling of urgency due to a full bladder. In time, these children learn to restrict fluids as a method of increasing voiding intervals.

Underactive bladder: This term replaces the term "lazy bladder" syndrome. These children, more commonly girls, present with a history of using Valsalva maneuvers to void. They have high bladder capacity, decreased

detrusor activity with an interrupted urinary stream with high post-void residuals. Some believe this to be the end result of chronic voiding postponement resulting in overstretched detrusor muscle and weak or absent contractions. These children are at risk for urinary tract infections due to incomplete emptying.

Dysfunctional voiding: "Dysfunctional voiding" is a unique condition under "Voiding dysfunction" and cannot be used interchangeably. It is defined as the inability to relax the external sphincter and/or pelvic floor muscles during voiding. It is diagnosed by observing uroflow curves in conjunction with electromyography of the sphincter. External sphincter activity is detected during a flow that is either slow or staccato in nature. These children are neurologically normal in contrast to children with detrusor-sphincter dyssynergia (DSD) who have neurologic lesions like neural tube defects or spinal cord injuries. Dysfunctional voiding is the same phenomenon as those previously described as having the classic Hinman–Allen syndrome.

These patients present with various complaints. These include frequency, urgency, straining, and incontinence due to incomplete emptying and increased detrusor activity. The high-pressure voiding and elevated post void residuals translates to increased frequency of urinary tract infection, upper tract damage with resultant renal damage, and bladder decompensation (*30*)

Vaginal Reflux/Voiding: Incontinence in small-moderate amount seen in girls within minutes after normal voiding mostly likely have vaginal reflux. Associated with no other symptoms, this is sometimes seen in overweight girls who void with legs close together leading to urine reflux into vagina and spillage upon standing up.

Giggle incontinence (GI): Uncontrollable complete voiding spontaneously occurs during or immediately after laughing. The child is otherwise asymptomatic and voiding is normal when the child is not laughing. Etiology being unknown, some postulate GI to be secondary to detrusor hyperactivity and treat with anticholinergics without overwhelming success (*31*). Theories for central nervous mediation like cataplexy have been proposed and have gained support by a report of positive treatment by methylphenidate, a central nervous system modulator (*32*).

Extraordinary daytime urinary frequency: This term is applied to children over 3 years of age with very high daytime voiding frequency –sometimes hourly – with low volumes. Nocturnal bladder behavior is normal and incontinence is uncommon. Corigliano (*33*) reported on 26 children with this symptom complex, normal flow, and negative urinary and found a history of recent emotional or psychosocial stress event in majority of these children. The condition is self limiting and often treated with reassurance and observation though anticholinergic agents may offer symptom relief. The median duration of symptoms was 5 months but longer in those with psychosocial issues.

EVALUATING CHILDREN WITH VOIDING DYSFUNCTION AND INCONTINENCE

History

A meticulous history is important to define the problem and plan effective management strategies. Questions should be age-appropriate and asked in a non-leading manner so as to accurately pinpoint the most troubling complaint from the patient's perspective. A good voiding history includes details of current voiding habits (timing, frequency, urgency nocturia, stream), incontinence and its type, posturing maneuvers (described or demonstrated) documented urinary tract infection, fluid intake and types, family history of similar problems, and social history (family dynamics, school or daycare issues). Questions should be made to address bowel habits including frequency, consistency, and encopresis. Other information to be elicited includes neurodevelopment, presence of ADD and toilet-training history. Current medications should be reviewed. A three-day food, voiding (Fig. 4.1), and defecation diary is useful in objectively quantifying the problem. Pain, incontinence of urine or feces, and urgency episode should all be documented in the diary. Past medical and surgical history is important regarding diabetes, psychiatric problems, prior urologic surgery, prior malignancies, etc.

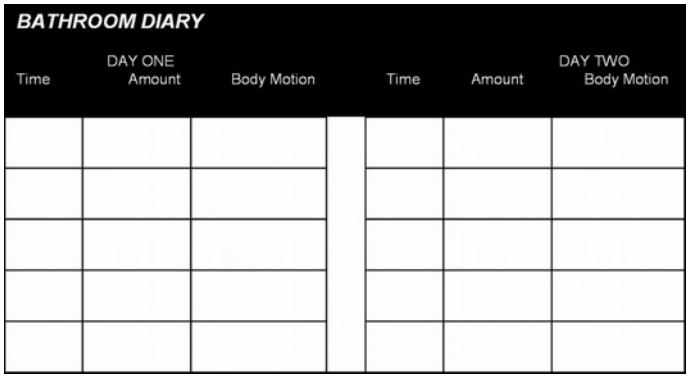

Fig. 4.1. Sample of a voiding diary to be filled out by the child and/or family. Careful recording allows the urologist to identify voiding patterns and should be coupled to a diary recording fluid and food intake.

Physical Examination

The goal of physical examination is to rule out any anatomical or neurological cause for voiding dysfunction. Toward this goal, physical examination should include the following:

– Neurologic exam – assessment of motor and sensory function of the lower extremity, perineal reflexes (anocutaneous reflex, perineal sensation).

- Abdomen/Back exam – signs of spinal dysraphism like sacral dimple, hair patch or a Mongolian spot as well as the presence of palpable stool, bladder, or masses.
- Genitourinary exam – In boys, it should include presence of foreskin, meatal stenosis, and other congenial anomalies of the penis. In girls, it should include inspection of introitus for presence of vulvovaginitis or labial adhesions, constant urinary incontinence, and/or any cloacal abnormalities.
- Rectal exam (as needed) – to assess constipation and evaluate anal sphincter tone.

Investigation

Urine analysis and urine culture: It is essential to rule out subclinical UTI in children with voiding dysfunction by performing a urine analysis and urine culture if needed. Urinary specific gravity and glucose detection may detect medical conditions masquerading as urinary frequency.

Radiological studies: The need for further diagnostic tests is determined by history and physical examination findings. Any complicating factor noted above like congenital urinary tract anomalies, recurrent UTIs, vesicoureteral reflux, neurological anomalies, continuous incontinence, and evidence of renal damage (casts and/or proteinuria) are indications for radiological examination. The appropriateness of the test depends on the pathology that is to be confirmed or refuted. A concise guide is as follows:

1. Ultrasound
   - detect duplex collecting system, ectopic ureter, hydronephrosis, renal scars
   - assess post void residuals – volume > 10% implies incomplete emptying
   - measurement of bladder wall thickness – increased thickness implies detrusor overactivity, high-pressure voiding, and bladder outflow obstruction
2. Voiding Cystourethrogram
   - should start with plain film (Fig. 4.2) to assess spine and possible constipation
   - important in all children with febrile or recurrent UTI to assess reflux, bladder emptying, and presence of urethral abnormalities (valves, stricture) (Fig. 4.3)
3. MRI
   - indicated in any child with signs of spinal dysraphism
   - in patients with neurological abnormalities on exam
   - treatment refractory voiding dysfunction
   - may be indicated in patients with impaired bladder sensation

Patch EMG – uroflow test: Children are asked to hold their urine until they feel a strong desire to void and then do so into a collection device that generates a flow curve based on the force of impact of urine. The study provides information about the flow time, voided volume, and maximum and average

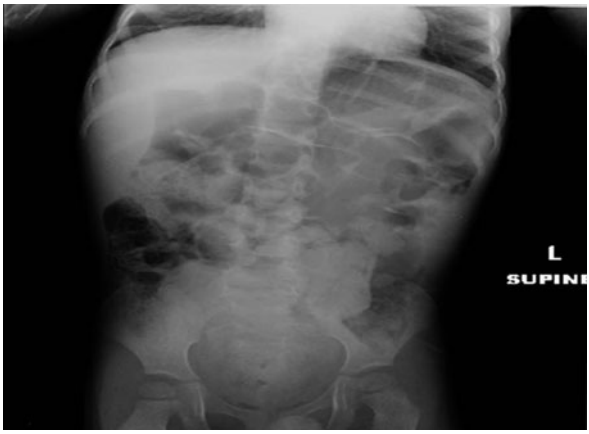

Fig. 4.2. Plain film of the abdomen demonstrating large amounts of stool. Evacuation of stool and maintenance of steady bowel movements helps avert voiding dysfunction, incontinence, and UTIs.

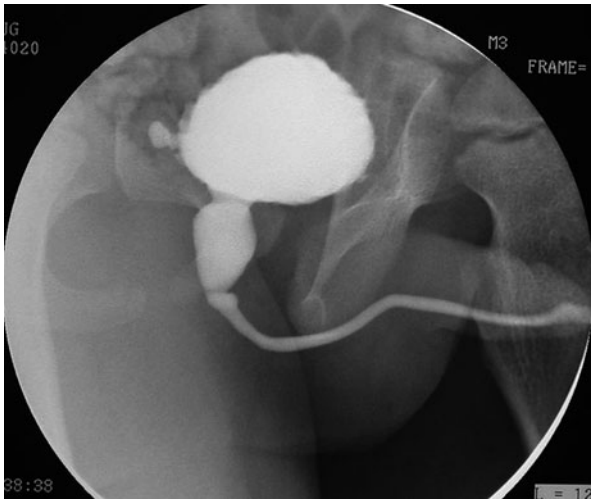

Fig. 4.3. VCUG in a boy with persistent daytime and nighttime incontinence. The diagnosis of posterior urethral valves is made by the cutoff in the posterior urethra leading to dilatation of the posterior urethra and hypertrophied bladder neck. The bladder is trabeculated and a small diverticulum is present.

flow rate. Patch or needle EMG electrodes are placed to correlate sphincter activity with flow curves to identify dysfunctional voiding (Fig. 4.4). Post void residual measurement is made by ultrasound.

Urodynamics: Formal urodynamic evaluation is more invasive than a patch EMG and uroflow. Accordingly, additional information is gleaned that can only be determined by reproducing the entirety of the filling and

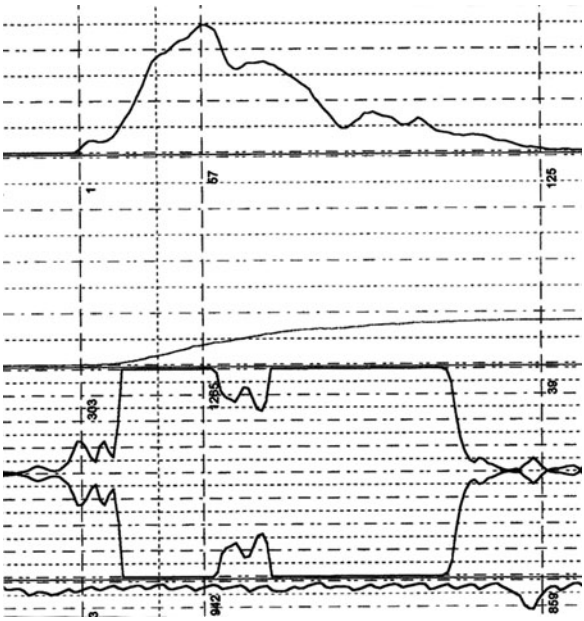

Fig. 4.4. EMG-Uroflow demonstrating a staccato voiding pattern and absence of the external urinary sphincter to relax.

emptying phases of urination. This additional information includes detrusor instability, incontinence, bladder pressure, bladder compliance, sphincter activity, and bladder emptying. Urodynamic evaluation is standard in the evaluation of bladder function among children with neural tube defects such as spina bifida and sacral agenesis as well as children with high imperforate anus, other spinal abnormality, or trauma including tethered cord syndrome (*34*). In children with posterior urethral valves, bladder exstrophy, cerebral palsy, severe dysfunctional voiding, or persistent nocturnal and diurnal enuresis, urodynamics may be necessary to assess function and modulate treatment plans.

Urodynamics in children is performed as in adults by catheterization of the bladder and rectum (Fig. 4.5). In general, a 7-Fr double-lumen urethral catheter is used in small children and a 10-Fr catheter in older children. The use of improper sized catheters can cause artifact with regards to flow, urethral resistance, and sphincter activity, and cause bladder irritation. The bladder is filled with warm saline or contrast (37°) at a rate of 10% of expected bladder capacity/minute. Bladder capacity is estimated according to the formula (age +2) × 30 (*35*). Bladder capacity estimates are different for children with neurogenic bladders (*36*). The measured parameters and their definitions are the same as in adults, i.e., compliance, P_{detrusor}, P_{bladder}, $P_{\text{abdominal}}$, first desire to void, uninhibited contractions, etc. The normal values in children are listed in Table 4.1.

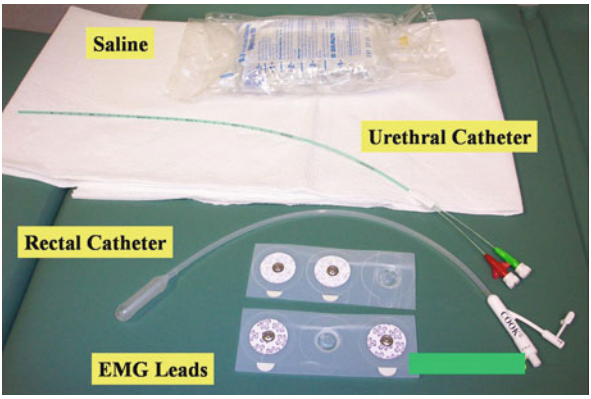

Fig. 4.5. Urodynamic evaluation requires the hardware items labeled in the photograph.

Table 4.1
Normal urodynamic parameters

Flow Rate (minimum)
Males:
4–7 yo = 10 ml/s when voiding 100 cc
8–13 yo = 12 ml/s when voiding 100 cc
≥14 yo = 21 ml/s when voiding 200 cc
Females:
4–7 yo = 10 ml/s when voiding 100 cc
8–13 yo = 15 ml/s when voiding 100 cc
>/=14 yo = 18 ml/s when voiding 200 cc
Voiding pressure:
Males:
55–80 cm H_2O
Females:
30–65 cm H_2O

The characteristic urodynamic findings in specific voiding include the following:

- Overactive bladder – Involuntary detrusor contraction, normal sphinter activity
- Dysfunctional voiding – Sphincter activity in voiding phase, some may have detrusor hyperactivity as well
- Underactive bladder – Weak detrusor contractions with large bladder capacity and large post void residual

The addition of video can be used when visualization of the bladder and the outlet is needed. These situations include (1) possible or known bladder outlet obstruction; (2) intractable incontinence; (3) neurogenic bladder; (4) known or possible bladder diverticulum or vesicoureteral reflux; (5) unclear diagnosis or conflict between prior studies and clinical assessment. The disadvantages include the use of ionizing radiation and the added cost (Fig. 4.6).

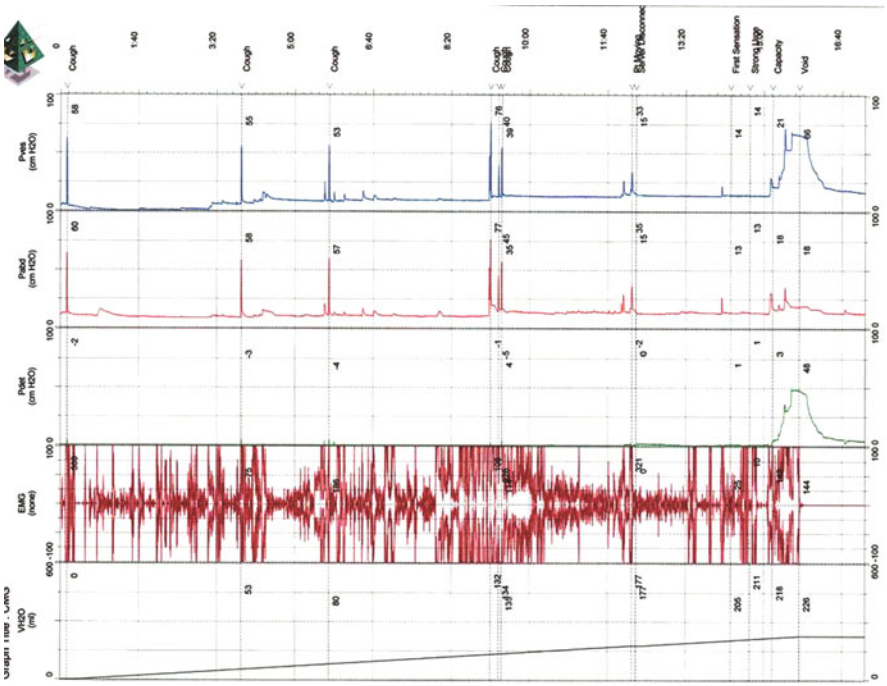

Fig. 4.6. An example of a urodynamic study in an incontinent child. The study is normal with low detrusor pressure, absence of abdominal pressure, absence of uninhibited contractions, and appropriate bladder contraction at capacity. The only abnormal finding is the contracted external sphincter noted through the first half of the bladder contraction.

Management

The goal of management in these children should be targeted at the underlying cause(s) of the child's voiding dysfunction. The causes should be determined in most cases after a careful history, examination, and investigation. The two main avenues of treatment are pharmacotherapy and non-pharmacological modalities. Treatment should be titrated for individual patients based on their type of voiding dysfunction, complications if present, and behavioral issues.

Patient and parental education is paramount for successful treatment of nocturnal enuresis. Children and their families are often confused about

enuresis and have a limited understanding of the anatomy and physiology of urine production, bladder function, and the nervous system. Parents should be educated that enuresis is not due to laziness or intention but rather a delayed maturational process between bladder and brain co-ordination. Involving the child in the management will preserve self-esteem and is of key importance for a successful outcome. A sequentially escalating treatment starting with non-pharmacological management is the recommended treatment.

Behavior modification: This has remained as one of the main stays of treatment of children with voiding dysfunction and encompasses several different factors. As in adults, avoiding diets laden with possible bladder irritants like coffee or soda, avoiding excessive fluid intake with voiding diaries have been shown to be helpful. Timed voiding (every 2 h) alone improves symptoms in one third of children with overactive bladder, urge incontinence, and dysfunctional voiding (*37*). A combination treatment of timed voiding, modification of fluid intake, positive reinforcement techniques, and pelvic floor exercises have been shown to improve 60% of children with daytime incontinence after a mean follow up of 4.7 years (*38*).

For children with nocturnal enuresis, behavior modification encompasses two complementary approaches. The first approach is to assure that the child modifies his/her food and toileting habits so as to avoid fluids after dinner, particularly irritants as mentioned above, and void before bedtime. The second approach employs a nocturnal wetting alarm to effect classic conditioning upon the child that is supplemented by positive reinforcement. The alarm attaches to the child's undergarments and is activated (auditory and/or vibratory) when there is wetness on the alarm. The alarm aims to awaken the child before the bladder is empty; the child then goes to the bathroom to finish emptying the bladder. With time, the child responds faster to the alarm leaving more urine in the bladder, and ultimately, the child responds to the full bladder before the alarm sounds. For the alarm to be effective, it typically requires at least 15 weeks of use. It should be used until the child achieves four straight weeks of dry nights. Wetting alarms have a high cure rate (75%) and comparatively low relapse rate (41%) (*39*, *40*). In children who relapse, a short course of treatment is successful (*41*). The disadvantages, household disturbance by loud auditory alarms and its duration, accounts for the 10–30% treatment drop-out rates (*42*).

Using a positive reinforcement chart or other consistent positive tokens representative of a successfully dry night helps to maintain use of the alarm and/or compliance with medications. Every night that the child is dry, he/she is offered a star marked in a chart in the child's room. When the child accumulates stars, they may be offered bigger incentives. This positive reinforcement requires extensive patient participation by the parents – understanding that in spite of treatment there are going to be wet nights. Studies have reported cure rates of 25% with positive reinforcement alone although improvements have been reported in up to 70% of patients (*9*, *39*).

Biofeedback: Biofeedback relies on creating a conscious realization of activity of pelvic floor muscles and training the child to relax these muscles during detrusor contraction. By real time monitoring of uroflow and EMG activity, children can be taught to identify dysfunctional sphincter/pelvic floor muscle contraction. They can also be taught to avoid these contractions by actively relaxing these muscles and hence treat dysfunctional voiding. Biofeedback training entails a keen interest and enthusiasm from the child and a dedicated, patient specially trained nurse. Biofeedback has been shown to be an excellent technique to manage children with dysfunctional voiding with a sustained improvement in the long term (*43*, *44*). The addition of animation to the EMG activity has proven to expedite the resolution of symptoms (*45*) (Fig. 4.7). In addition, biofeedback has been shown to hasten the resolution or at least downgrade vesicoureteral reflux in girls with dysfunctional voiding (*46*).

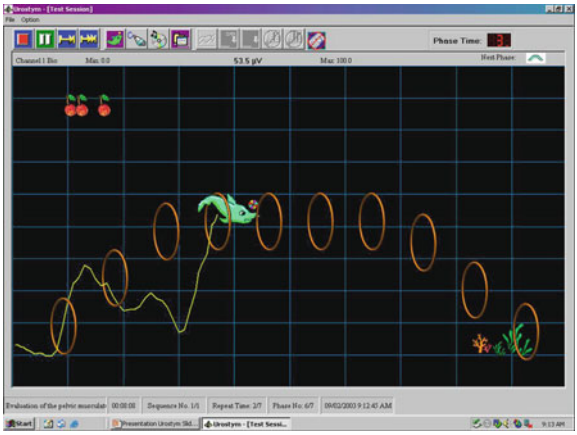

Fig. 4.7. An example of the animated screen available for biofeedback. Child-driven EMG activity leads to the vertical movement of the dolphin. The goal is to learn to modulate the external sphincter by guiding the dolphin through the hoops. After satisfactory control is gained, the child learns to relax the sphincter at will. These techniques are then used when the child voids.

Management of constipation: Constipation has long been associated with voiding dysfunction and UTI. In a study of 234 chronically constipated encopretic children, comparison of voiding dysfunction and UTI before and 12 months after effective treatment of constipation showed 100% resolution of recurrent UTI, 89% reduction in daytime incontinence, and 63% reduction in night time incontinence (*47*).

Bowel management should be part of any treatment strategy in children with voiding dysfunction. The aim of treatment is (A) to evacuate any existing impaction of stool in the colon and (B) to maintain regular painless bowel movements with soft stools. The initial evacuation is performed by a combination of oral laxatives and rectal enemas. Subsequently, regular pain free

soft bowel movements are achieved by diet modifications (high fiber food, increased water intake), supplemental fiber, and oral laxatives.

Pharmacotherapy: Bladder modulators through autonomic nervous system form the central theme for pharmacological therapy. This can be used alone or in conjunction with the behavioral modalities discussed above.

Anticholinergics: Anticholinergics can effectively treat urgency and urge incontinence in by decreasing detrusor overactivity and increase functional bladder capacity. It has been used intravesically in children with neurogenic bladders (*48*). The more commonly used antimuscarinics are oxybutynin and tolterodine in either short acting or longer acting formulations. The safety profile of tolterodine is thought to be better than oxybuytnin (4 vs 10%) because it is more bladder specific (*49*). The safety and efficacy including long-term efficacy of antimuscarinic agents particularly tolterodine has been shown in multiple studies (*50*, *51*). Combination of anticholinergics and behavioral modification has been reported to be more efficacious than either treatment alone (*52*).

Alpha-adrenergic antagonists: Increased bladder outlet resistance due to primary bladder neck dysfunction has been recently recognized in children. It is characterized on EMG-Flow studies by delayed bladder neck opening time and on videourodynamics as incomplete bladder neck funneling, elevated PVR, and silent EMG. This condition responds well to alpha-adrenergic blockade with improved flow rates, decreased PVR (*53*, *54*), and symptom relief (*55*).

Desmopressin: A synthetic analogue of ADH, this drug decreases the amount of urine made after intake and hence aims to prevent the child from reaching functional residual capacity. The oral formulation is widely used. Treatment is continued for 3–6 months and then slowly weaned to assess treatment result (*56*). Desmopressin is most effective in children older than 9 years and in children with minimum symptoms (*57*). Twenty-five percent of children achieved complete dryness, whereas 10–90% achieved significant reduction in number of wet nights. Relapse rates are as high as 80–100% (*58*). Side effects are uncommon but behavioral changes and nightmares have been reported (*56*).

Tricyclic antidepressants: Although tricyclic antidepressants (TCA) have shown to be effective in patients with nocturnal enuresis, evidence is lacking for its use in daytime voiding dysfunction. TCAs acts centrally by altering sleep cycles and possibly by stimulating pituitary secretion of ADH (*59*) and locally with anticholinergic effects resulting in decreased detrusor action and a central effect. It acts within 2 h of ingestion and effects last for up to 8–12 h. Initial treatment response is judged at around 2 weeks and the dose adjusted according to the clinical response or tolerance of side effects Treatment durations should be between 3 and 6 months. Success rates are as high as 50%; however, 50% of the responders relapse after stopping treatment (*39*). Side effects include dry mouth, insomnia, arrhythmia, and personality changes.

Combination therapy for nocturnal enuresis: Combination of behavioral therapy with desmopressin has been shown to improve symptoms in patients who failed individual treatments and in patients with treatment compliance issues (*60*, *61*).

Botulinum toxin: Botulinum toxin has been used in children with voiding dysfunction. The injection is into the detrusor muscle at the bladder base or at the external sphincter. Several studies have demonstrated improvement in detrusor overactivity, continence, PVR, and UTI development (*62*, *63*).

Clean Intermittent Catheterization

In children with persistent problems, particularly with high residual volumes leading to recurrent UTI, clean intermittent catheterization may be the final resort to assure bladder emptying, decrease UTI, and regain continence (*64*).

Surgical Management

Children with extremes of voiding dysfunction with resultant high-pressure bladder with outlet obstruction with or without upper tract reflux may require bladder augmentation with or without a bladder outflow procedure. Augmentation cystoplasty with continent diversion such as a Mitrofanoff procedure might be the final treatment option in children with severe dysfunctional voiding.

CONCLUSIONS

The general urologist needs to be familiar with pediatric voiding dysfunction and incontinence. The importance of a thorough history and physical examination cannot be over-emphasized. In most cases, these alone will divulge the important factors that need to be addressed. In other cases, additional testing such as imaging and urodynamic studies will be needed to supplement the history and physical examination. Treatment strategies should address specific etiologic factors. These strategies may as simple as behavior modification of fluid intake or may require biofeedback in the dysfunctional voider or nocturnal wetting alarm for the enuretic child. Other children, day- or night-wetters, may require pharmacotherapy. The impact of effecting a cure or significant improvement in voiding dysfunction has an overwhelmingly positive effect on the children and their families.

REFERENCES

1. Neveus, T., von Gontard, A., Hoebeke, P., Hjalmas, K., Bauer, S., Bower, W., Jorgenson, T.M., Rittig, S., Walle, J.V., Yeung, C., Djurhuus, J.C. (2006) The standardization of terminology of lower urinary tract function in children and adolescents: Report from the standardization committee of the International Children's Continence Society. J Urol 176: 314–24.

2. Hoebeke, P. (2002) Voiding dysfunction, recurrent UTI, constipation and vesico-ureteral reflux: A common disease complex. Dialogues Pediatr Urol 25(8): 1–8.
3. Rushton, H.G. (1995) Wetting and functional voiding disorders. Urol Clin North Am 22: 75–93.
4. Hinman, F., Baumann, F.W. (1973) Vesical and ureteral damage from voiding dysfunction in boys without neurologic or obstructive disease. J Urol 109: 727–32.
5. Miller, K. (1993) Concomitant nonpharmacologic therapy in the treatment of primary nocturnal enuresis. Clin Pediatr [Phila] July(Spec No): 32–7.
6. Yeung, C.K., Godley, M.L., Ho, C.K., Ransley, P.G., Duffy, P.G., Chen, C.N. (1995) Some new insights into bladder function in infancy. Br J Urol 76: 235–40.
7. Brazelton, T.B., Christophersen, E.R., Frauman, A.C., Gorski, P.A., Poole, J.M., Stadtler, A.C., Wright, C.L. (1999) Instruction, timeliness and medical influences affecting toilet training. Pediatrics 103: 1353–8.
8. Jansson, U.B., Hanson, M., Sillen, U., Hellstrom, A.L. (2005) Voiding pattern and acquisition of bladder control from birth to age 6 years – a longitudinal study. J Urol 174: 289–93.
9. Schmitt, B.D. (1997) Nocturnal enuresis. Pediatr Rev 18: 183–91.
10. Bailey, J.N., Ornitz, E.M., Gehricke, J.G., Gabikian, P., Russell, A.T., Smalley, S.L. (1999) Transmission of primary nocturnal enuresis and attention deficit hyperactivity disorder. Acta Paediatr 88: 1364–8.
11. Norgaard, J.P., Djurhuus, J.C., Watanabe, H., Stenberg, A., Lettgen, B. (1997). Experience and current status of research into the pathophysiology of nocturnal enuresis. Br J Urol 79: 825–35.
12. Bakwin, H. (1971) Enuresis in twins. Am J Dis Child 121: 222–5.
13. Eiberg, H., Berendt, I., Mohr, J. (1995) Assignment of dominant inherited nocturnal enuresis (ENUR1) to chromosome 13q. Nat Genet 10: 354–6.
14. Whitside, C.G., Arnold, E.P. (1975) Persistent primary enuresis. Urodynamic assessment BMJ 1(5954), 364–7.
15. Troup, C.W., Hodgson, N.B. (1971) Nocturnal functional bladder capacity in enuretic children. Wis Med J 70: 171–3.
16. Norgaard, J.P., Hansen, J.H., Nielsen, J.B., Rittig, S., Djurhuus, J.C. (1989) Nocturnal studies in enuretics. A polygraphic study of sleep-EEG and bladder activity. Scand J Urol Nephr 125, 73–8.
17. Norgaard, J.P., Hansen, J.H., Wildschlotz, G., Sorenson, S., Rittig, S., Djurhuus, J.C. (1989) Sleep cystometries in children with nocturnal enuresis. J Urol 141: 1156–9.
18. Norgaard, J.P., Pederson, E.B., Djurhuus, J.C. (1985) Diurnal antidiuretic hormone levels in enuretics. J Urol 134(5): 1029–31.
19. Wille, S. (1984)Nocturnal enuresis: Sleep disturbance and behavior patterns. Acta Paediatr 83: 772–4.
20. Kawauchi, A., Watanabe, H., Miyoshi, K. (1996) Early morning urine osmolality in nonenuretic and enuretic children. Pediatr Nephrol 10: 696–8.
21. Wolfish, N.M., Pivik, R.T, Busby, K.A. (1997) Elevated sleep arousal thresholds in enuretic boys: clinical implications. Acta Pediatr 86: 381–4.
22. Watanabe, H., Azuma, Y. (1989) A proposal for a classification system of enuresis based on overnight simultaneous monitoring of electroencephalography and cystometry. Sleep 12: 257–64.
23. Fergusson, D.M., Horwood, L.J. (1994) Nocturnal enuresis and behavior problems in adolescence: A 15-year longitudinal study. Pediatrics 94(5): 662–8.
24. Sureshkumar, P., Craig, J.C., Roy, L.P., Knight, J.F. (2000) Daytime urinary incontinence in primary school children: a population-based survey. J Pediatr 137: 814–8.
25. Robson W.L. (1997) Diurnal enuresis. Pediatr Rev 18: 407–12.
26. Hellerstein, S., Zguta, A.A. (2003) Outcome of overactive bladder in children. Clin Pediatr (Phila) 42: 553–6.
27. Vincent S.A. (1966) Postural control of urinary incontinence. The curtsy sign. Lancet 2: 631–2.

28. Hellström, A.L., Hanson, E., Hansson, S., Hjälmås, K., Jodal, U. (1990) Micturition habits and incontinence in 7-year-old Swedish school entrants. Eur J Pediatr 149(6): 434–7.
29. Hellström, A., Hanson, E., Hansson, S., Hjälmäs, K., Jodal, U. (1995) Micturition habits and incontinence at age 17 – reinvestigation of a cohort studied at age 7. Br J Urol 76(2): 231–4.
30. Hinman, F. Jr. (1986) Nonneurogenic neurogenic bladder (the Hinman syndrome) – 15 years later. J Urol 136: 769–77.
31. Chandra, M., Saharia, R., Shi, Q., Hill, V. (2002) Giggle incontinence in children: a manifestation of detrusor instability. J Urol 168: 2184–7.
32. Sher, P.K., Reinberg, Y. (1996) Successful treatment of giggle incontinence with methylphenidate. J Urol 156: 656–8.
33. Corigliano, T., Renella, R., Robbiani, A., Riavis, M., Bianchetti, M.G. (2007) Isolated extraordinary daytime urinary frequency of childhood: a case series of 26 children in Switzerland. Acta Paediatr 96: 1347–9.
34. Palmer, L.S., Richards, I., Kaplan, W.E. (1998) Subclinical changes in bladder function in children presenting with non-urologic symptoms of tethered cord syndrome. J Urol 159:231–4.
35. Koff , S.A. (1983) Estimating bladder capacity in children. Urology. 21:248.
36. Palmer, L.S., Richards, I., Kaplan, W.E. (1997) Age-related bladder capacity and bladder capacity growth in children with myelomeningocele. J Urol 158: 1261–4.
37. Hellström, A.L., Hjälmås, K., Jodal, U. (1987) Rehabilitation of the dysfunctional bladder in children: method and 3-year follow-up. J Urol 138: 847–9.
38. Wiener, J.S., Scales, M.T., Hampton, J., King, L.R., Surwit, R., Edwards, C.L. (2000) Long-term efficacy of simple behavioral therapy for daytime wetting in children. J Urol 164: 786–90.
39. Monda, J.M., Husmann, D..(1995) Primary nocturnal enuresis: A comparison among observation, imipramine, desmopressin acetate and bedwetting alarm systems. J Urol 154: 745–8.
40. Friman, P.C. (1995) Nocturnal enuresis in the child. In: Ferber R, Kryger MH, eds. Principles and practice of sleep medicine in the child. Philadelphia: Saunders, 107–13.
41. Cutting, D.A., Pallant, J.F., Cutting, F.M. (2007) Nocturnal enuresis: application of evidence-based medicine in community practice. J Paediatr Child Health 43: 167–72.
42. Graziottin, A., Chiozza, M.L. (1994) Nocturnal enuresis: social aspects and treatment perspectives in Italy – a preliminary report. Scand J Urol Nephrol Suppl 163: 21–8.
43. Porena, M., Costantini, E., Rociola, W., Mearini, E. (2000) Biofeedback successfully cures detrusor-sphincter dyssynergia in pediatric patients. J Urol 163: 1927–31
44. Bower, W.F., Yew, S.Y., Sit K.Y.F., Yeung, C.K. (2006) Half-day urotherapy improves voiding parameters in children with dysfunctional emptying. Eur Urol 49: 570–4
45. Kaye, J.D., Palmer, L.S. (2008) Animated biofeedback yields more rapid results than non-animated biofeedback in the treatment of external sphincter overactivity in the pediatric population. J Urol 180: 300–5.
46. Palmer, L.S., Franco, I., Rotario, P., Reda, E.F., Friedman, S.C., Kolligan, M.E. (2002) Biofeedback therapy expedites the resolution of reflux in older children. J Urol 168: 1699–702.
47. Loenig-Baucke ,V. (1997) Urinary incontinence and urinary tract infection and their resolution with treatment of chronic constipation of childhood. Pediatrics 100: 228–32.
48. Palmer, L.S., Zebold, K., Firlit, C.F., Kaplan, W.E. (1997): Complications of intravesical oxybutynin chloride therapy in the pediatric myelomeningocele population. J Urol 157: 638–40,
49. Kilic, N., Balkan, E., Akgoz, S., Sen, N., Dogruyol, H.. (2006) Comparison of the effectiveness and side effects of tolterodine and oxybutynin in children with detrusor instability. Int J Urol 13: 105–8.
50. Nijman, R.J. (2004) Role of antimuscarinics in the treatment of nonneurogenic daytime urinary incontinence in children. Urology 63: 45–50.

51. Hjalmas, K. (1992) Functional daytime incontinence: pharmacological treatment. Scand J Urol Nephrol Suppl 141: 108–14.
52. Ayan, S., Topsakal, K., Gokce, G., Gultekin, E.Y. (2007). Efficacy of combined anticholinergic treatment and behavioural modification as a first line treatment for nonneurogenic and nonanatomical voiding dysfunction in children: a randomized control trial. J Urol 177: 2325–9.
53. VanderBrink, B.A., Gitlin, J., Toro, S., Palmer, L.S. (2009). Effect of tamsulosin on systemic blood pressure and nonneurogenic dysfunctional voiding in children. J Urol 181(2): 817–22.
54. Donohoe, J.M., Combs, A.J., Glassberg, K.I. (2005). Primary bladder neck dysfunction in children and adolescents II: results of treatment with alpha adrenergic agonists. J Urol 173: 212–6.
55. Cain, M.P., Wu, S.D., Austin, P.F., Herndon, C.D., Rink, R.C. (2003). Alpha blocker therapy for children with dysfunctional voiding and urinary retention. J Urol 170: 1516–7.
56. Tullus, K., Bergstrom, R., Fosdal, I., Winnergard, I., Hjalmas, K. (1999) Efficacy and safety during long-term treatment of primary monosymptomatic nocturnal enuresis with desmopressin. Swedish Enuresis Trial Group. Acta Paediatr 88: 1274–8.
57. Moffatt, M.E., Harlos, S., Kirshen, A.J., Burd ,L. (1993) Desmopressin acetate and nocturnal enuresis: how much do we know? Pediatrics 92: 420–5.
58. Matthiesen, T.B., Rittig, S., Djurhuus, J.C., Norgaard, J.P. (1994) A dose titration, and an open 6-week efficacy and safety study of desmopressin tablets in the management of nocturnal enuresis. J Urol 151: 460–3.
59. Puri, V.N. (1986). Increased urinary antidiuretic hormone excretion by imipramine. Exp Clin Endocrinol 88: 112–4.
60. Sukhai, R.N., Mol, J., Harris, A.S. (1989). Combined therapy of enuresis alarm and desmopressin in the treatment of nocturnal enuresis. Eur J Peds 148: 465–7.
61. Ilyas, M., Jerkins, G. (1996). Management of nocturnal childhood enuresis in managed care: A new challenge. Ped Ann 25: 258–64.
62. Hoebeke, P., De Caestecker, K., Vande Walle, J., Dehoorne, J., Raes, A., Verleyen, et al. (2006) The effect of botulinum-A toxin in incontinent children with therapy resistant overactive bladder. J Urol 176: 328–30.
63. Steinhardt, G.F., Naseer, S., Cruz, O.A. (1997) Botulinum toxin: novel treatment for dramatic urethral dilatation associated with dysfunctional voiding. J Urol, 158: 190–1.
64. Pohl HG, Bauer SB, Borer JG, Diamond DA, Kelly MD, Grant R, Briscoe CJ, Doonan G, Retik AB (2002). The outcome of voiding dysfunction managed with clean intermittent catheterization in neurologically and anatomically normal children. BJU Int 89: 923–7.

5 Hematuria: Gross and Microscopic

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Abstract The etiology of hematuria in the pediatric population is varied and ranges from infections, trauma, medical renal diseases, and urolithiasis, to congenital urologic conditions and, rarely, malignancies of the urinary tract. More often than not, hematuria in children is caused by medical rather than surgical processes. Hematuria may be characterized as microscopic or macroscopic (gross) and may be present with or without proteinuria. Although microscopic hematuria is much more common than macroscopic hematuria, the yield of an extensive work-up for isolated microscopic hematuria is low. Children with persistent isolated microhematuria should be evaluated with a urine Ca/Cr ratio, parental urinalysis, and annual renal function tests and blood pressure measurements to ensure that they do not develop hypertension or significant proteinuria. Children with gross hematuria should undergo a complete evaluation with CBC, serum C3 and C4, BUN, creatinine, potassium, ASO titers, coagulation parameters, and autoantibody titers such ANA, pANCA, cANCA, dsDNA, and anti-GBM in the setting of a relevant family history. Renal-bladder ultrasound is also recommended, along with renal biopsy for glomerulonephropathy. Invasive tests such as cystoscopy should be reserved for cases where the preceding work-up is inconclusive. Urologic referral is indicated when the work-up is suggestive of an anatomic abnormality, tumor, calculus, trauma, or recurrent macroscopic hematuria of undetermined origin. In contrast, the presence of hematuria in association with hypertension, proteinuria, hypocomplementemia, systemic disease, or a family history of renal disease almost always warrants referral to a nephrologist.

Keywords Hematuria · Dipstick · Glomerulophritis · Nephropathy · Urolithiasis · Nephrolithiasis · Stones · Hypercalciuria · Proteinuria · IgA nephropathy · Alport's · Systemic lupus erythematosus · Henoch-Schonlein purpura · Goodpasture's · Hemolytic-uremic syndrome · Nephrocalcinosis · Nephritis · Renal cysts · Wilms' · Renal injury · Genitourinary trauma · Renal mass · Sickle-cell ·

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Renal vein thrombosis · Cystitis · Hydronephrosis · Urinary tract infection · Urethrorrhagia

INTRODUCTION

Hematuria is one of the most important signs of renal and bladder disease. The detection of even microscopic amounts of blood in a child's urine can cause great alarm to the patient, parents, and the physician, and prompt the performance of many diagnostic studies. The etiology of hematuria in the pediatric population is varied and ranges from infections, trauma, medical renal diseases, and urolithiasis, to congenital urologic conditions and, rarely, malignancies of the urinary tract. More often than not, hematuria in children is caused by medical rather than surgical processes.

The American Academy of Pediatrics recommends that a screening urinalysis be obtained in all children during child care visits at 5 years of age, and once again during the second decade of life. The evaluation and management of asymptomatic microscopic hematuria detected on routine screening is significantly different from that of macroscopic hematuria that develops spontaneously, and is also dependent on accompanying symptomatology.

This chapter discusses the epidemiology and common etiologies of hematuria in children, and illustrates a systematic approach to evaluation and management, with an aim to detect significant and treatable problems in this population and to avoid unnecessary testing.

DEFINITION

Hematuria is defined as the presence of five or more red blood cells (RBCs) per high-power field (HPF) on a freshly voided centrifuged urine sample. However, even normal children can excrete RBCs in urine in the setting of exercise or fever. Most authors, therefore, recommend that at least two of three urinalyses show evidence of hematuria over a period of 2–3 weeks before further evaluation is performed.

In the clinical setting, the evaluation of hematuria usually begins with a urinary "dipstick" test which utilizes a peroxidase-like chemical reaction between hemoglobin or myoglobin and the chemical indicator compound impregnated on the stick. The sensitivity and specificity of the dipstick method for detecting blood in the urine varies. However, when tested on urine samples in which a predetermined amount of blood had been added, urine dipsticks were found to have a sensitivity of 100% and a specificity of 99.3%, even when tested on urine 4 h after void (*1*). False-negative results may occur in the presence of formalin, used as a urine preservative, or high urinary concentrations of ascorbic acid (*2*). False-positive results can be seen in a child with fever or after exercise, or in the presence of menstrual blood or alkaline urine with a pH greater than 9. Additionally, the use of oxidizing

agents such as peroxidase to clean the perineum before obtaining a urine specimen can also contribute to false-positive results. Microscopic analysis of 10–15 mL of freshly centrifuged urine is thus essential to confirm the diagnosis of hematuria suggested by a positive dipstick.

Urine discoloration without the presence of RBCs is seen in several conditions (Table 5.1). Heme-positive urine without intact red blood cells is caused by the presence of free hemoglobin or myoglobin. Hemoglobinuria commonly occurs in the presence of intra-vascular hemolysis. Myoglobinuria is the result of rhabdomyolysis syndrome due to skeletal muscle injury and is generally associated with a five-fold increase in the plasma concentration of creatinine kinase. Conditions predisposing to rhabdomyolysis include viral myositis, crush injury, severe electrolyte abnormalities, disseminated intravascular coagulation, certain toxins, and prolonged seizures. Pigmenturia, or heme-negative urine, may appear red, cola-colored, burgundy, dark brown, or even black depending on the ingestion of certain food or drugs, or the excretion of various urinary metabolites (Table 5.1). A negative urinary dipstick test eliminates the possibility of hemoglobin or myoglobin as the etiology of urinary discoloration.

Table 5.1
False-positive tests for hematuria

	Heme negative (Pigmenturia)		
Heme positive	*Drugs*	*Dyes*	*Metabolites*
Hemoglobin Myoglobin	Chloroquine Deferoxamine Ibuprofen Iron sorbitol Metronidazole Nitrofurantoin Pyridium Rifampin Salicylates Sulfasalazine	Beets Blackberries Food coloring	Homogenistic Acid Melanin Methemoglobin Porphyrin Tyrosine Urates

Urine centrifugation and microscopic analysis can be helpful in localizing the source of bleeding. After centrifugation, a red-brown sediment with a clear supernatant indicates the presence of whole blood in urine. On the contrary, if the sediment is not discolored and the supernatant is red-brown, then urine discoloration is more likely due to free myoglobin or hemoglobin. On microscopic examination, findings such as red cell casts are pathognomonic for glomerular disease. Red blood cells with a dysmorphic appearance, particularly acanthocytes, are also more likely to have a glomerular origin. Although helpful if present, the absence of these findings does not rule out

glomerular disease. In non-glomerular hematuria, microscopic examination reveals urinary RBCs with a uniform size and shape. Hypercalciuria, a non-glomerular cause of hematuria can be associated with dysmorphic red blood cells, but not red blood cell casts (Table 5.2).

Patients and parents should be reassured that the degree of color change of the urine does not necessarily reflect the degree of blood loss. While just one milliliter of blood per liter is sufficient to induce a visible color change, hematuria in children is almost never a cause of anemia.

CLASSIFICATION

Hematuria may be characterized as microscopic or macroscopic (gross). It may present with or without additional clinical symptoms to help localize its source. These symptoms often include lower urinary tract irritation, such as dysuria, frequency, urgency, and bladder spasms, as well as the presence of clots in the urine. Alternatively, symptoms of glomerular disease may be described, including edema, arthralgia, or rash. Patients with glomerular disease are also more likely to present with hypertension, elevated serum creatinine, anemia, and hypoalbuminemia.

Depending on the etiology, hematuria may or may not present with proteinuria. Plasma proteins are excreted in urine in proportion to the degree of bleeding. As much as 2+ protein can be detected by dipstick analysis during episodes of gross hematuria, solely from hemolysis of urinary erythrocytes. The presence of greater than 2+ protein in the urine raises suspicion of glomerular disease, especially when hypoalbuminemia is also present. Evaluation of the degree of proteinuria is important, as the presence of significant proteinuria with hematuria is associated with a higher risk of morbidity than hematuria alone (*3*, *4*).

Additionally, hematuria may be transient, intermittent, or persistent. It may be present for either the initial or terminal portion, or for the entire duration of the urinary stream. Based on all of the above considerations, four categories of hematuria have been proposed: gross hematuria, microscopic hematuria with clinical symptoms, asymptomatic isolated hematuria, and aysmptomatic hematuria with proteinuria (*5*).

EPIDEMIOLOGY

Most studies of hematuria in children have been conducted by screening healthy children, or by retrospective analyses of children with hematuria, usually comprising cases from a single health center. These studies demonstrate that although microscopic hematuria is much more common than macroscopic hematuria, pathologic findings in microscopic hematuria are much less frequent.

Vehaskari et al. screened an unselected population of 8,954 children aged 8–15 years for hematuria by examining four urine samples from each child.

Table 5.2
Distinguishing features of glomerular and non-glomerular hematuria

Feature	*Glomerular hematuria*	*Non-glomerular hematuria*
1. History		
• Irritative voiding symptoms	• Usually absent	• Dysuria, frequency, urgency, bladder spasms
• Systemic complaints	• Headache, nausea, vomiting, abdominal pain, cough, hemoptysis, rash	• Fever, nausea, vomiting, abdominal pain
• Family history	• IgA nephropathy, SLE, Alport's, Benign familial hematuria	• Cystic disease, Nephrocalcinosis, Tumors, Sickle cell disease, Coagulopathies, Hypercalciuria, Urolithiasis
2. Physical examination		
• Hypertension	• Present	• Usually absent
• Edema	• Present	• Usually absent
• Abdominal mass	• Usually absent	• Renal mass, Hydronephrosis, Cystic disease
• Rash	• Present	• Usually absent
• Arthralgia	• Present	• Usually absent
• Elevated creatinine	• Present	• May be present with significant urinary tract obstruction
• Anemia	• Present	• Usually absent
• Hypoalbuminemia	• Present	• Usually absent
3. Urinalysis		
• Color	• Cola-colored/brown	• Red/pink
• Proteinuria	• Present	• Usually not significant
• Dysmorphic red blood cells	• Present	• May be present with hypercalciuria
• Red blood cell casts	• Present	• Usually absent

Microscopic hematuria was detected in one or more specimens in 4.1% of the children. However, hematuria was transient in the majority of these children, and after excluding children who had only one positive urine sample, the prevalence of microscopic hematuria was calculated to be 1.1% (*6*). In contrast to some other contemporary reports, prevalence was not age or sex dependent. The most common identifiable etiology was urinary tract infection (6%), followed by UPJ obstruction (1.6%), IgA nephropathy (1.6%), and Alport's syndrome (0.8%). The overall prevalence of proteinuria in the same population was 10.6%, while the prevalence of hematuria and proteinuria combined was 0.7%.

In a prospective study of the natural history of microhematuria by Hisano et al., 251 of 160,000 unselected Japanese schoolchildren screened (0.15%) were found to have isolated microscopic hematuria. The authors excluded from this group all children with an identifiable cause, namely, menstruation (35%), UTI (5.6%), hypercalciuria (2%), HSP (1.2%), hydronephrosis (1.2%), and polycystic kidney disease (0.4%). The remaining 136 children were observed along with their parents over a period of 7.4 years. Nineteen of these children underwent renal biopsy for concern of glomerular disease, with IgA nephropathy being the most common pathologic finding. At the end of the study period, 26% of children had resolution of hematuria, 74% had persistent isolated microhematuria, and less than 1% had microhematuria with proteinuria. Most importantly, no children in this study developed any clinical or laboratory evidence of renal insufficiency. The authors concluded that isolated microscopic hematuria is a relatively benign condition after the exclusion of easily identifiable causes, which has a good long-term prognosis, and does not necessitate renal biopsy (*7*).

Similar findings have been reported after retrospective analyses of microscopic hematuria. Feld et al. reviewed the charts of 325 children referred to a tertiary care facility for an evaluation of microscopic hematuria. Study subjects were selected after the application of strict exclusion criteria, including history of proteinuria, nephrolithiasis, systemic illness, glomerular disease, sickle cell disease, bleeding diatheses, and presence of UTI. All laboratory and radiologic studies performed were reviewed. Seventy-eight percent of patients had serum chemistries analyzed, and all values were found to be normal for age. Complement levels were checked in 48% of children, and despite low levels in two children, further work-up for proteinuria, hypertension, or impaired renal function was negative. Eighty-seven percent of children had renal ultrasounds performed, and 28% underwent VCUGs. Only 18 ultrasound exams were abnormal, and none showed clinically significant findings. Nine VCUGs were abnormal, and showed low-grade reflux. The results of this study clearly demonstrated the low yield of a detailed work-up for isolated hematuria (*8*). The latter is an important point to consider in light of the cost of a complete evaluation for hematuria, which can average between $500–1,000 per individual (Table 5.3).

Table 5.3
Etiology of isolated microscopic hematuria

Common causes
IgA nephropathy
Alport's syndrome
Post-streptococcal glomerulonephritis
Thin glomerular basement membrane disease
Henoch-Schonlein purpura nephritis
Sickle cell trait or disease
Idiopathic hypercalciuria
Urolithiasis
Less common causes
Membranous glomerulonephritis
Membranoproliferative glomerulonephritis
SLE-associated glomerulonephritis
Coagulopathies and thrombocytopenia
Arteriovenous malformations
Trauma
Obstruction
Tumor
Exercise
Fever

Gross hematuria in children is relatively uncommon, and accounts for approximately 1.3 in 1000 outpatient visits to a pediatrician (*9*). Various etiologies may account for gross hematuria, including infections, glomerulopathies, stones, hematologic disorders, and tumors, but the relative frequency of these known causes varies depending upon the clinical setting (Table 5.4). A 2-year retrospective review of 150 patients presenting to a tertiary pediatric emergency center with gross hematuria found that documented (26%) or suspected (23%) urinary tract infection was the underlying diagnosis in more than half of all patients (*9*). Only 9% of patients in this study population had apparent glomerular disease. In contrast, in a 10-year retrospective review of 342 children with gross hematuria presenting to a pediatric urologic center, the most common causes were urethrorrhagia (19%), trauma (14%), and UTI (14%) (*10*). In this study, there were no cases of glomerular disease, which illustrates the difference in the population of patients seen in an ambulatory general pediatric setting versus a specialty office setting. Further illustrating this point is a third retrospective case series of 100 patients from a pediatric nephrology center where gross hematuria secondary to a glomerular cause was identified in 29% of the patients, with IgA nephropathy and Alport syndrome being the most common diagnoses (*11*).

Table 5.4
Etiology of macroscopic (gross hematuria)

Glomerular
Post-streptococcal glomerulonephritis
IgA nephropathy
Alport's syndrome
Thin glomerular basement membrane disease
Membranous glomerulonephritis
Membranoproliferative glomerulonephritis
SLE-associated glomerulonephritis
Henoch-Schonlein purpura nephritis
Rapidly progressive crescentic glomerulonephritis
Goodpasture's disease
Hemolytic-uremic syndrome
Interstitial
Cystic disease
Nephrocalcinosis
Interstitial nephritis
Acute tubular necrosis
Cortical necrosis
Nephrotoxins
Tumors
Vascular
Trauma
Sickle cell nephropathy
Renal vein thrombosis
Renal artery thrombosis
Coagulopathies and thrombocytopenia
Arteriovenous malformations
Nutcracker syndrome
Lower Urinary Tract
Glomerular
Idiopathic hypercalciuria
Nephrolithiasis
Bacterial infection
Hemorrhagic cystitis
Obstruction
Urethrorrhagia
Heavy exercise
Loin pain-hematuria syndrome

In the two referral-based retrospective studies above, boys were at a higher risk for gross hematuria than girls, likely due to their increased susceptibility to trauma of the urethral meatus. In the study by Ingelfinger et al., there was no sex predilection with respect to the prevalence of gross hematuria when the total population was considered. However, females predominated in the subgroup of patients with documented and suspected urinary tract infections, while patients with recurrent gross hematuria, trauma, or meatal stenosis were predominantly male.

Unlike patients with isolated microhematuria, patients with gross hematuria usually require extensive evaluation, as the underlying diagnosis is more often clinically significant. Laboratory studies, as well as imaging modalities such as ultrasound and VCUG, are useful in order to establish a definitive diagnosis. Cystourethroscopy may be used in cases where gross hematuria persists despite negative radiologic findings. Renal biopsy is also recommended and useful when indicated.

ETIOLOGY

Hematuria in children is more frequently due to medical rather than surgical causes and can result from involvement of the glomerulus, renal interstitium, renal vascular supply, or lower urinary tract.

HEMATURIA FROM GLOMERULAR CAUSES

Although glomerular causes of hematuria are typically painless, some patients do complain of vague abdominal or flank pain upon presentation. Hematuria may be either microscopic or macroscopic. Approximately 10% of all children with gross hematuria have either an acute or chronic form of glomerulonephritis, the most common causes being IgA nephropathy and poststreptococcal glomerulonephritis (*2*). When glomerular bleeding leads to microscopic hematuria, it is usually accompanied by proteinuria.

Acute Post-streptococcal Glomerulonephritis

Acute post-streptococcal glomerulonephritis (PSGN) is a classic example of the acute nephritic syndrome characterized by the sudden onset of gross hematuria, edema, hypertension, and renal insufficiency. After IgA nephropathy, acute PSGN is the next most common cause of glomerular hematuria in children. The development of PSGN follows 1–2 weeks after streptococcal pharyngitis or 3–6 weeks after streptococcal skin infections with certain nephritogenic strains of group A beta-hemolytic streptococci.

PSGN is most common in children aged 5–12 years and uncommon before the age of three years. At the time of presentation, patients may be asymptomatic, or complain of malaise, headache, nausea, vomiting, abdominal pain, and oliguria. Depending on the severity of renal involvement,

physical examination often reveals edema and hypertension. Hypertensive encephalopathy may be seen in up to 10% of cases. Urinalysis reveals proteinuria with hematuria. Red blood cell casts, if present, help confirm the diagnosis. Serum BUN and creatinine can be normal or elevated. The C3 component of the complement pathway is almost always decreased, while C4 is usually normal or only mildly depressed. Renal biopsy is not necessary for the diagnosis of PSGN, but should be considered if macroscopic hematuria, proteinuria, diminished renal function, or low C3 levels persist for longer than 2 months after onset.

Confirmation of the diagnosis of PSGN requires clear evidence of invasive streptococcal infection, in order to rule out other diagnoses such as systemic lupus erythematosus and an acute exacerbation of a chronic glomerulonephritis. An elevated antistreptolysin-O titer is common after a pharyngeal infection but rarely increases after streptococcal skin infections. Documentation of cutaneous infections is best done with anti-DNAase B titers.

Treatment of PSGN is supportive and includes management of its potential complications such as hypertension, acidosis, electrolyte disturbances, and uremia. Early systemic antibiotic therapy for streptococcal infections unfortunately does not eliminate the risk of glomerulonephritis. The ultimate prognosis of PSGN is good; complete recovery occurs in more than 95% of children. The acute phase of the disease generally resolves within 6–8 weeks, accompanied by resolution of proteinuria and hypertension, and return of C3 to baseline levels. Microscopic hematuria, however, can persist for 1–2 years after initial presentation.

IgA Nephropathy

IgA nephropathy remains the most common chronic glomerular disease worldwide. It commonly presents with recurrent gross hematuria that begins 1–2 days after the onset of a respiratory or gastrointestinal illness and resolves in 5–7 days. Patients with IgA nephropathy can also have asymptomatic but persistent microscopic hematuria and proteinuria without gross hematuria.

The pathophysiology of this disease remains elusive, although some recent research has linked IgA nephropathy to chromosome 6q22-23, and family clustering of the disease has also been described (*12*). IgA nephropathy is seen more often in males than females. Affected children require close, long-term follow-up. Approximately 25% of these patients develop a slowly progressive deterioration in renal function in adulthood, whereas the remaining 75% remain stable or improve (*13*). Poor prognostic indicators include persistent hypertension, diminished renal function, and heavy or prolonged proteinuria. Hisano et al. followed the clinical course of 43 Japanese children with IgA nephropathy and found that disease outcome correlated with the level of proteinuria and the severity of renal pathology on biopsy

specimens. In particular, children with proteinuria >1 g/m^2/day had moderate to severe histological findings, and half of these patients developed hypertension or renal insufficiency during the follow-up period (*14*).

Besides the urinary findings of hematuria, proteinuria, and RBC casts, the results of other laboratory investigations such as serum C3, are usually in the normal range. Serum IgA levels are only elevated in 15% of patients and have no diagnostic value. A renal biopsy is required for diagnosis. The primary treatment is blood pressure control along with reduction in proteinuria. ACE inhibitors are currently considered first line agents due their beneficial effects on both conditions. Other advocated therapies include corticosteroids, mycophenolate mofetil, and fish oil, but their efficacy in preserving renal function in children is unproven.

Alport's Syndrome

Alport's syndrome, or hereditary nephritis, is caused by mutations in the gene for Type IV collagen, a major component of the glomerular basement membrane. Depending on the type of mutation involved, inheritance of this syndrome may be X-linked, autosomal recessive, or autosomal dominant. The majority of patients (85%) have X-linked disease, secondary to a mutation in the COL4A5 gene encoding the α-5 chain of Type IV collagen. All patients have asymptomatic microscopic hematuria with some degree of proteinuria, and approximately 50% of patients develop self-limiting episodes of gross hematuria 1–2 days after an upper respiratory infection. Progressive proteinuria, often exceeding 1 g/day is common by the second decade of life and can be severe enough to cause nephrotic syndrome.

Extrarenal manifestations of Alport's syndrome include sensorineural hearing loss and ocular abnormalities. A careful family history of renal failure or premature hearing loss, urinalysis of first-degree relatives, an audiogram, and ophthalmologic examination are therefore key components of the work-up of this syndrome.

In boys, Alport's syndrome progresses to end-stage renal disease faster than in girls, due to the X-linked transmission of Alport's syndrome. Risk factors for progression are nephrotic syndrome, gross hematuria in childhood, and prominent glomerular basement membrane thickening on biopsy. No specific therapy for this disease in available, although some studies have used cyclosporine and ACE inhibitors with good effect (*2*). Dialysis and renal transplantation are the only options for definitive therapy.

Thin Glomerular Basement Membrane Disease

Thin glomerular basement membrane (GBM) disease is defined by the presence of asymptomatic, typically microscopic hematuria with isolated thinning of the glomerular basement membrane on electron microscopy. Physical examination and laboratory values are all within normal limits. When isolated microhematuria presents in this fashion in multiple family

members without any evidence of renal disease, the condition is also referred to as benign familial hematuria.

Thin GBM disease can be sporadic or transmitted as an autosomal dominant trait in the familial form. Because the pathological features of benign familial hematuria resemble those of Alport's syndrome, a common molecular defect has been proposed. Using linkage analysis, Badenas et al. have described that mutations in the COL4A4 and COL4A3 genes, implicated in Alport's syndrome, also have a role in families with benign familial hematuria (*15*).

The diagnosis of thin GBM disease or benign familial hematuria is one of exclusion. Renal biopsy is usually not necessary. Prognosis is excellent; however, most authors recommend that these children be followed on an annual basis to assess for the development of proteinuria, hypertension, renal insufficiency, or other signs and symptoms that negate the diagnosis of thin GBM disease and suggest the presence of Alport's syndrome.

Membranous Glomerulonephritis

Although the most common cause of nephrotic syndrome in adults, membranous glomerulopathy is an uncommon cause of hematuria in children. It generally occurs in the second decade of life, although a neonatal form has been reported. The presentation is that of nephrotic syndrome, and most patients only develop microscopic hematuria. Membranous glomerulopathy accounts for 2–6% of childhood nephrotic syndrome cases.

Diagnosis is confirmed by renal biopsy, as there are no specific diagnostic tests. Indications for biopsy include nephritic syndrome, or the presence of unexplained hematuria and proteinuria. Affected patients are at risk for renal vein thrombosis. Prognosis of membranous glomerulonephritis is variable, but patients with asymptomatic, low-grade proteinuria and microhematuria can have spontaneous remission.

Membranoproliferative Glomerulonephritis

Membranoproliferative glomerulonephritis (MPGN) is typically idiopathic in the pediatric population and presents with microscopic hematuria with proteinuria in up to 35% of affected children. In adults, it may be associated with systemic cryoglobulinemia. Other presentations include nephrotic syndrome with renal insufficiency (35%), chronic, progressive glomerulonephritis (20%), and a rapidly progressive glomerulonephritis with renal failure and red cell casts (10%). It is most common in the second decade of life and rare under the age of five. MPGN predominantly affects Caucasians, with no obvious sex predilection. Three distinct histological classifications of MPGN are defined (types I, II, and III), which may be associated with various abnormalities of the immune system as well as chronic infections like Hepatitis B and C.

Complement levels are depressed, and unlike post-streptococcal glomerulonephritis, do not return to normal. Diagnosis is often confirmed by renal biopsy. Treatment is based on the severity of histologic injury and on the degree of proteinuria, typically consisting of a prolonged course of oral steroids. MPGN carries a poor prognosis in children, with 40–50% of affected patients progressing to end stage renal disease over 10 years.

Glomerulonephritis Associated with Systemic Lupus Erythematosus

Renal involvement is one of the most common features of systemic lupus erythematosus (SLE) in childhood and may occasionally be the only manifestation. The majority of children with SLE are adolescent females. Clinical evidence of renal disease occurs in 30–70% of affected children. The severity and treatment of SLE nephritis are variable, and determined by the World Health Organization renal histologic classification.

The diagnosis of SLE is based on detecting antibodies specific for native, double-stranded DNA. C3 and C4 levels are also depressed. However, because the correlation between clinical manifestations of the disease and renal involvement is so variable, renal biopsy is recommended in all patients with SLE. Immunosuppressive therapy is the cornerstone of treatment for SLE nephritis, and aggressive therapy has been shown to improve the prognosis of SLE in childhood. Success of therapy is defined as normalization of levels of C3, C4, and anti-dsDNA antibodies and reduction in proteinuria. Depending on the histologic classification and disease severity, prednisone, azathioprine, mycophenolate mofetil, cyclophosphamide, and monoclonal anti CD20 antibody (rituximab) have all been used as immunosuppressive agents.

Henoch-Schonlein Purpura Nephritis

Henoch-Schonlein Pupura (HSP) is a small vessel vasculitis, characterized by a pupuric rash, arthritis, abdominal pain, and glomerulonephritis (Fig. 5.1). The exact pathogenesis of this disease is unknown, but the mechanism involves formation of immune complexes containing polymeric IgA within capillaries of the skin, intestines, and glomerulus. Predictably, renal biopsy findings in HSP are identical to those seen in IgA nephropathy; however, systemic findings including the characteristic skin rash involving the buttocks and lower extremities are only encountered in HSP nephritis.

Renal manifestations of HSP may occur several weeks after the initial presentation of HSP. Gross hematuria is seen in 20–30% of cases, but patients may also present with microscopic hematuria with or without proteinuria. Nephritic syndrome, nephrotic syndrome, and acute renal insufficiency are all less frequent. Ureteritis, an uncommon urologic manifestation of HSP, is seen in children younger than 5 years of age. HSP may result in ureteral

Fig. 5.1. Penoscrotal erythema and characteristic lower extremity rash seen in Henoch-Schonlein Purpura.

stenosis with subsequent hydronephrosis and flank pain, requiring surgical correction.

The risk of developing chronic renal disease secondary to HSP nephritis is 2–5%. Prognosis is best in the setting of isolated microscopic hematuria. Presentation with acute nephritic or nephrotic syndrome carries the highest risk of developing hypertension, hematuria, or chronic renal failure. Treatment is supportive; controlled data showing that any specific therapy reduces the risk of progression to severe renal disease is lacking.

Rapidly Progressive Crescentic Glomerulonephritis

Although rare, rapidly progressive glomerulonephritis (RPGN) is one of the few emergencies in pediatric nephrology. Initial presentation is similar to post-streptococcal glomerulonephritis, with gross hematuria, edema, and hypertension, but prognosis is considerably worse. The most common causes of RPGN include anti-GBM disease, and ANCA antibody-associated vasculitis. IgA nephropathy, SLE, PSGN, and HSP can occasionally have a rapidly progressive phenotype, or RPGN can be idiopathic.

Appropriate serologic studies include anti-GBM antibody, c-ANCA, p-ANCA, antinuclear antibodies, C3 levels, and anti-DNAase B titers, in order to delineate the specific underlying cause. Renal function studies show renal insufficiency and associated electrolyte abnormalities. Renal biopsy is necessary to confirm the diagnosis and characteristically demonstrates glomerular crescents and widespread interstitial inflammation.

Most patients develop acute renal failure associated with acute nephritic or nephrotic syndrome typically associated with severe hypertension. Progression to renal failure can occur within weeks to months after onset. Children with a rapidly progressive course associated with PSGN usually recover

with treatment. A combination of high-dose prednisone and cyclophosphamide therapy may lead to a therapeutic response with SLE nephritis, IgA nephropathy, and HSP nephritis, if initiated early. Plasmaphresis is reserved for patients presenting with anti-GBM disease or ANCA-associated vasculitis. Despite aggressive therapy, renal outcomes in RPGN are less favorable, and end-stage renal disease develops within 2–3 years.

Goodpasture's Disease

Goodpasture's disease, or anti-glomerular basement membrane nephritis, is characterized by pulmonary hemorrhage and glomerulonephritis associated with antibodies against specific epitopes of type IV collagen, which is found within alveolar and glomerular basement membranes.

Renal manifestations include acute nephritic syndrome with hematuria, proteinuria, and hypertension. Progressive renal failure can occur within weeks to months. Detection of anti-GBM antibodies is sufficient to confirm the diagnosis. Pulmonary hemorrhage associated with this condition can be life-threatening. Patients who survive pulmonary hemorrhage usually progress to end-stage renal failure. However, with the use of pulse methylprednisolone, oral cyclophosphamide, and plasmapheresis, improvement has been seen in rates of recovery of renal function if therapy is initiated early in the course of the disease.

Hemolytic-Uremic Syndrome

Hemolytic-uremic syndrome is the most common cause of acute renal failure in young children, classically characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia and uremia. HUS is associated with a variety of bacterial and viral infection, *E. coli* and Shigella being the most common, as well as several medications. The most typical presentation is that of an acute enteritis with diarrhea, caused by Shiga-like toxin produced by *E. coli* O157:H7, found in undercooked meat and unpasteurized milk. The toxin is absorbed from the intestines and initiates endothelial cell injury in glomeruli and small arteries and arterioles.

HUS is most common in children younger than 4 years of age. Physical examination may reveal dehydration, edema, petechiae, hepatosplenomegaly, and marked irritability. Renal manifestations vary from mild renal insufficiency to acute oliguric or anuric renal failure requiring dialysis. Patients with bilateral renal vein thrombosis may be difficult to clinically distinguish from those with HUS. A Doppler ultrasound can help with the diagnosis of renal vein thrombosis. A renal biopsy for the diagnosis of HUS is rarely indicated.

HEMATURIA DUE TO RENAL INTERSTITIAL DISEASES

Renal interstitial causes of hematuria can be sub-classified into a number of categories, including infectious and metabolic causes, medications and toxins, and anatomic and neoplastic abnormalities.

Cystic Disease

Renal cysts may be solitary and simple, or associated with multicystic dysplasia or polycystic kidney disease (Figs. 5.2 and 5.3). Cystic disease is the most common renal anatomic abnormality associated with hematuria. Dilatation and distortion of the renal parenchyma can lead to flank pain and brisk bleeding, in part because of urokinase production by the kidneys. Cystic disease-associated hematuria can, therefore, require immediate urologic or nephrologic evaluation.

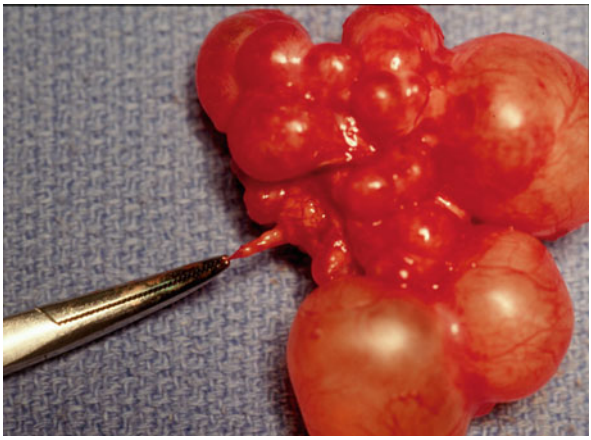


Fig. 5.2. Multicystic dysplastic kidney disease.

Nephrocalcinosis

Nephrocalcinosis is defined as an increase in the calcium content of the kidney. There are numerous causes of nephrocalcinosis, including renal tubular acidosis, hypercalciuria, loop diuretics, hyperparathyroidism, medullary sponge kidney, prolonged immobilization, as well as a number of inherited metabolic disorders (Figs. 5.4 and 5.5). Renal calcification induces renal tubular and interstitial damage, leading to microscopic or gross hematuria. The clinical significance and the prognosis of nephrocalcinosis remains unclear, although the degree of nephrocalcinosis has been negatively correlated with glomerular filtration rate and concentration capacity (*16*).

Fig. 5.3. Multiple bilateral renal cysts.

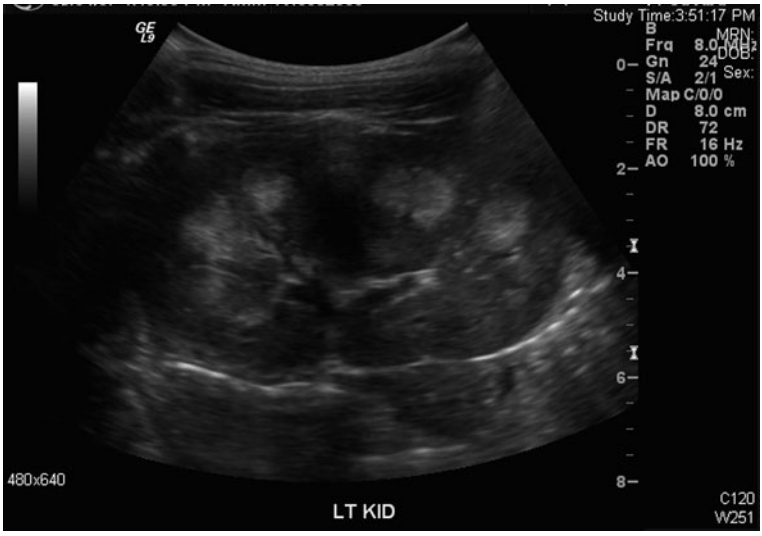


Fig. 5.4. Diffuse nephrocalcinosis.

Interstitial Nephritis

Interstitial nephritis in characterized by tubulointerstitial inflammation and damage, with relative sparing of the glomeruli and vessels. Both acute and chronic forms of this condition exist. Causes include a variety of medications, primary glomerular diseases, as well as systemic diseases such as lupus erythematosus.

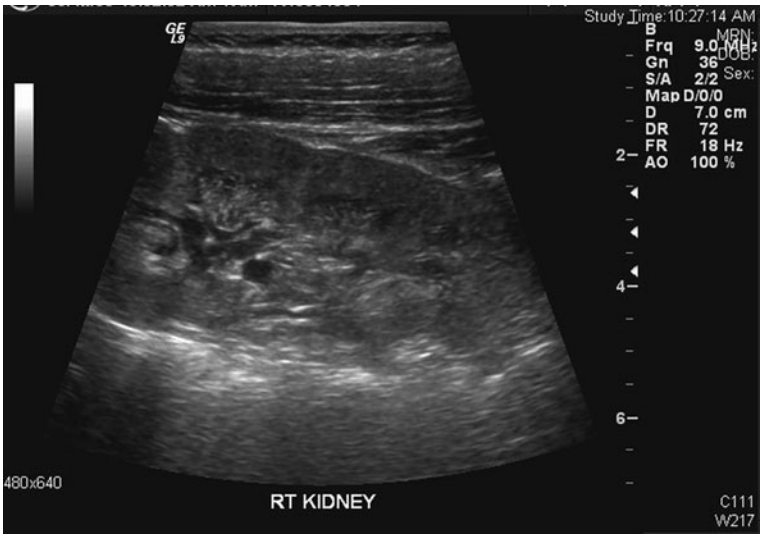


Fig. 5.5. Linear pattern of nephrocalcinosis involving the collecting ducts of the renal parenchyma.

The classic presentation of interstitial nephritis is fever, rash, and arthralgia, in the setting of a rising serum creatinine. Patients may additionally complain of non-specific constitutional symptoms, such as nausea, vomiting, and fatigue, or specific signs and symptoms of a systemic disease like SLE. Sterile pyuria is an important diagnostic clue. Eosinophilia and eosinphiluria is occasionally present. Some degree of microscopic hematuria is invariably present, but significant hematuria or proteinuria is uncommon. One exception is patients with NSAID-induced interstitial nephritis, who may present with nephrotic syndrome. Treatment is supportive, and directed at addressing the complications of acute renal failure and cessation of the offending medication, if present. Steroids may help shorten the duration of renal failure.

Acute Tubular Necrosis

Renal hypoperfusion and renal ischemia are the most commonly documented causes of acute tubular necrosis, although various endogenous and exogenous nephrotoxic agents are also recognized. The mechanism of injury in acute tubular necrosis (ATN) includes alteration in intrarenal hemodynamics, tubular obstruction, and passive backleak of glomerular filtrate across injured tubular cells into the peritubular capillaries.

The initial presentation is that of acute renal failure with oliguria. The urine sediment typically consists of brownish pigmented granular casts (“muddy brown casts”). Microscopic and occasional gross hematuria may also be present. The treatment of ATN revolves around management of fluid

status and renal function, during the initial oliguric phase as well as the later diuretic phase.

Cortical Necrosis

Renal cortical necrosis is the final common result of several types of renal injury, which develops when endothelial cell injury occurs in conjunction with diminished renal cortical blood flow. Toxins and other mediators that develop in this setting initiate intrarenal coagulation, leading to thrombosis and cortical necrosis. As such, renal cortical necrosis is most commonly seen in children with septic shock or severe hemolytic uremic syndrome. Cortical necrosis is also seen in newborns, where it is most commonly associated with ischemic insults secondary to perinatal asphyxia, placental abruption, and twin–twin or fetal–maternal transfusion syndromes.

Cortical necrosis presents as acute renal failure, with diminished urine output. Gross or microscopic hematuria may also be present. Hypertension is common, and thrombocytopenia may also be present as a result of renal microvascular injury. Therapy is aimed at managing the acute renal failure as well as treating the underlying etiology. Children with cortical necrosis may have little or no renal recovery. Prognosis therefore depends on the amount of surviving, uninvolved renal cortex.

Nephrotoxins

Medications, chemicals, and diagnostic agents such as iodinated radiographic contrast media can cause renal damage by a number of different mechanisms, including alteration of renal blood flow, intratubular obstruction, acute tubular necrosis, or induction of a hypersensitivity reaction. Depending upon the mechanism of nephrotoxicity, either gross or microscopic hematuria can signify renal injury. Nephrotoxiciy is often reversible if the offending agent is promptly identified and removed.

Tumors

Although uncommon in the pediatric population, tumors of the urinary tract are the primary concern for the parents of a child with hematuria. Of the pediatric tumors involving the urinary tract, Wilms tumor or nephroblastoma is most commonly associated with hematuria. It is a complex embryonal neoplasm of the kidney composed of blastemal, epithelial, and stromal elements (Fig. 5.6). While most cases are sporadic, 1–2% are familial, with autosomal dominant inheritance. Mutations of WT1, beta-catenin, and p53 genes are most commonly described. Several syndromes and congenital abnormalities are known to be associated with Wilms' tumor; genitourinary abnormalities include hypoplasia, ectopia, and fusion of the kidney, duplication of the collecting system, hypospadias, and cryptorchidism.

Wilms tumor accounts for 6% of pediatric cancers and is the second most common malignant tumor of childhood. It usually occurs in children aged

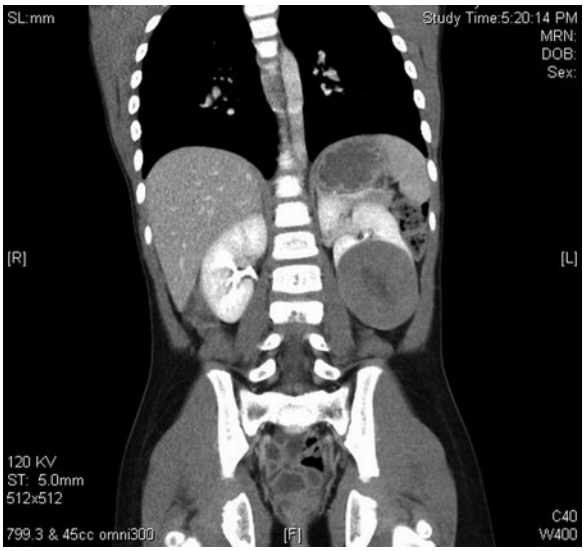


Fig. 5.6. Wilms' tumor involving lower pole of left kidney.

2–5 years, but has been encountered in neonates, adolescents, and young adults. Classic presentation is that of a palpable abdominal mass. Some patients also complain of abdominal pain and vomiting. Hematuria is seen in 12–25% of cases. Treatment consists of a combination of surgical extirpative therapy, chemotherapy, and radiation therapy. Prognosis depends on tumor size, stage, histologic subtype, and response to therapy. Overall, more than 60% of patients with Wilms tumor survive. Cure rate improves to more than 90% for lower stage tumors.

Although much less common than Wilms tumor, renal cell carcinoma and renal medullary carcinoma have also been reported in the pediatric population. Renal call carcinoma can present as hematuria with or without an abdominal mass. If detected early, complete resection of the tumor can achieve cure. In contrast, the prognosis of renal medullary carcinoma is much poorer. The latter is a highly aggressive tumor associated with sickle cell trait, and usually presents with hematuria and a flank mass. Metastasis is usually present at the time of diagnosis.

Any abdominal mass in a child must, therefore, be considered malignant until laboratory findings and diagnostic imaging prove otherwise. If the diagnosis remains unclear despite a complete evaluation, then biopsy of the mass is indicated.

VASCULAR CAUSES OF HEMATURIA

With the exception of trauma, vascular causes of hematuria in children are much less common than the other causes described here. However, many of

these are associated with gross hematuria, and are therefore more likely to be a source of concern for patients and their families.

Trauma

Hematuria can be the initial presenting sign of trauma to the urinary tract. Blunt trauma accounts for approximately 90% of pediatric renal injuries, with the remainder caused by penetrating injury. Injuries to the kidney occur in 10–20% of all cases of pediatric blunt abdominal trauma (*17*). The lack of perirenal fat, relatively larger size of the pediatric kidney in relation to the rest of the body, and decreased protection from the less ossified and more pliable thoracic cage are possible explanations for why children are more susceptible to renal injuries (*18*).

Urinalysis should be performed at each initial trauma evaluation, as a guide for further work-up. The need for additional imaging is based on the number of RBC/hpf and the type of trauma. Greater than 50 RBC/hpf in blunt trauma and greater than 5RBC/hpf in penetrating trauma are considered significant to warrant additional imaging (Fig. 5.7). However, the degree of renal injury cannot be determined by the presence, absence, or amount of hematuria. Several studies have reported gross hematuria in minor, grade I renal injuries, and minimal or no hematuria in severe, grade IV–V renal injuries (*17*).

Over the past two decades, the management of pediatric renal trauma has shifted toward conservative management, with preservation of renal parenchyma becoming the standard of care. With this approach, renal

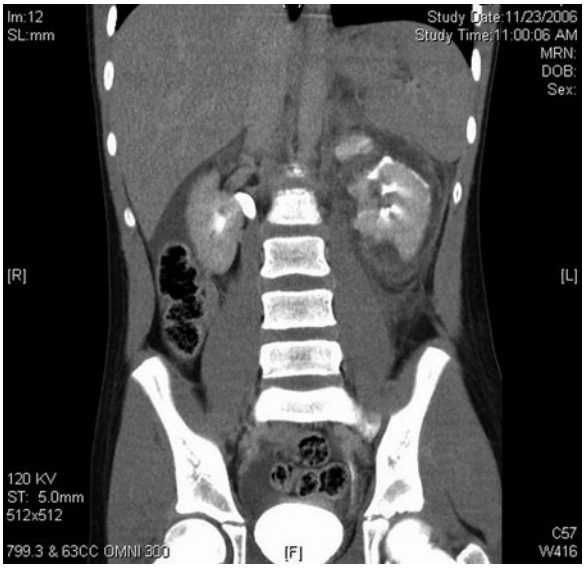


Fig. 5.7. Left renal laceration with subcapsular hematoma.

salvage rates of 98–99% have been reported in the recent literature (*19*). According to the current guidelines of the American Association for the Surgery of Trauma (AAST), hemodynamically stable grade I–III injuries can be managed non-operatively with hospital admission, strict bed rest, and serial examinations and hematocrits until complete resolution of hematuria. Grade IV–V renal injuries require selective management based on clinical presentation, hemodynamic stability, mechanism of injury, and other associated non-urologic injuries. Thirty to eighty percent of cases of severe grade IV–V injuries are associated with significant non-urologic injuries, which often precludes conservative management and may require operative intervention. In the absence of significant associated injuries, persistent bleeding is the primary reason for urological intervention.

Sickle Cell Nephropathy

After trauma, sickle cell nephropathy is the most prevalent vascular cause of hematuria. Both gross and microscopic hematuria can be seen in children with sickle cell disease or trait. Hematuria is thought to result from microthrombosis secondary to sickling in the relatively hypoxic, acidic, and hypertonic renal medulla.

In a prospective study of children with sickle cell disease, the prevalence of gross and microscopic hematuria was 1 and 16%, respectively (*20*). Sickle-cell associated hematuria is usually painless, episodic, of variable severity, and unilateral, occurring more commonly on the left side. Ultrasound imaging may show evidence of renal papillary necrosis. Obliteration of renal vasculature can lead to glomerular scarring and interstitial fibrosis over time.

Gross hematuria usually responds to hydration, but microhematuria can persist.

Additional clinical manifestations of sickle cell nephropathy include polyuria, renal tubular acidosis, and proteinuria. ACE inhibitors and hydroxyurea are used to decrease urinary protein excretion. No specific treatment for microhematuria exists in these patients.

Renal Vein Thrombosis

The development of renal vein thrombosis is suggested by the sudden onset of gross hematuria accompanied by unilateral or bilateral flank masses. Patients may also present with microscopic hematuria, flank pain, oliguria, or hypertension. Renal vein thrombosis (RVT) occurs in two distinct clinical situations, with impaired renal blood flow thought to be the common etiology. In newborns and infants, RVT is usually associated with birth asphyxia, shock, sepsis, dehydration, prolonged delivery, prematurity, and infants born to diabetic mothers. Among older children, RVT is seen more often in patients with nephrotic syndrome, cyanotic heart disease, and following exposure to angiographic contrast agents.

Fig. 5.8. Clot associated with renal vein thrombosis extending into the inferior vena cava.

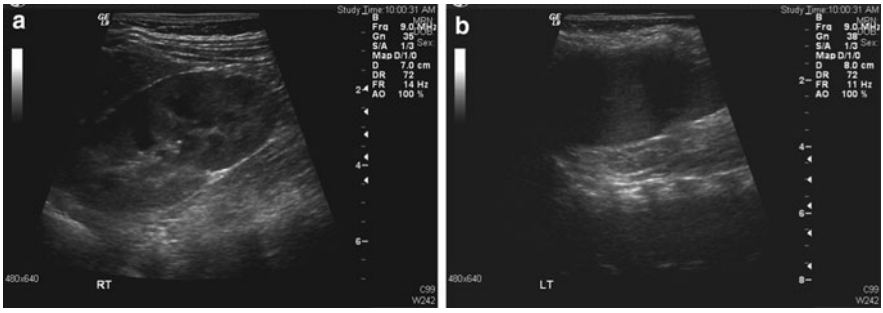


Fig. 5.9. (**a**) Long-term follow-up of left renal vein thrombosis demonstrates normal right kidney. (**b**) Long-term follow-up of left renal vein thrombosis demonstrates atrophic left kidney.

RVT begins in the intrarenal venous circulation and may spread to the renal vein and inferior vena cava (Figs. 5.8 and 5.9a, b). Thrombus formation is the result of endothelial injury due to hypoxia, endotoxins, or contrast media. Hypercoagulability due to conditions such as nephrotic syndrome, or mutations in genes encoding for clotting factors, can be a contributing factor. Approximately 20% of infants with gross hematuria are found to have renal vein thrombosis. Among neonates with RVT, approximately 20% have

bilateral involvement, and up to 50% may have pro-thrombotic tendencies (*21*). All patients with RVT should be screened for congenital and, in older children, acquired hypercoagulable states.

Diagnosis is best made on ultrasound imaging, which shows renal enlargement on the affected side, and may even demonstrate the thrombus. Alternatively, Doppler studies of the inferior vena cava and renal vein confirm the diagnosis. If performed, radionuclide studies reveal little or no function in the affected kidney. Bilateral RVT, therefore, usually results in acute renal failure.

The management of RVT is initially aimed at correcting fluid and electrolyte abnormalities. These children should be carefully followed for the development of hypertension. Specific treatment remains more controversial. The use of anticoagulation and thrombolytic agents such as heparin and streptokinase have been described, but are associated with significant complications. Surgical options such as thrombectomy and nephrectomy may be required for patients with IVC thrombosis and severe hypertension resistant to medications, respectively.

Renal Artery Thrombosis

The combination of hypertension and hematuria in a neonate suggest the possibility of renal artery thrombosis. Most cases of renal artery thrombosis involve umbilical artery catheterization, with the risk of thrombosis approaching 10%. Thrombotic involvement of the aorta may also be present. Diagnosis is made by ultrasound examination.

Management of this condition depends upon the clinical setting. The majority of unilateral cases are best managed expectantly. Control of hypertension is of foremost importance, with antihypertensive medications or nephrectomy, if necessary for treatment of resistant cases. The use of thrombolytic therapy has been described but is uncommon (*22*). The incidence of renal artery thrombosis has decreased over time, largely due to more selective and cautious use of umbilical artery catheterization.

Coagulopathies and Thrombocytopenia

Either gross or microscopic hematuria may be associated with inherited or acquired disorders of coagulation, such as hemophilia, von Willebrand's disease, disseminated intravascular coagulation, or thrombocytopenia. In these cases, however, hematuria is usually not the presenting complaint, and develops only after other manifestations of the disease.

Arteriovenous Malformations

Vascular abnormalities such as hemangiomas, angiomyomas, and arteriovenous malformations of the kidneys and lower urinary tract are rare causes of hematuria. Renal arteriovenous malformations are also known to occur rarely after renal biopsy. They typically present with gross hematuria with

the passage of blood clots. Renal colic may develop if the upper tract is involved. Cystoscopy in the setting of active bleeding may help demonstrate bleeding from one ureteral orifice, and thus help lateralize the lesion. Diagnosis is confirmed by angiography.

Nutcracker Syndrome

Nutcracker syndrome refers to compression of the left renal vein between the aorta and the superior mesenteric artery that results in elevation of pressure in the left renal vein and the subsequent development of collateral veins. Hematuria is believed to be caused by minute rupture of these thin-walled collateral veins into the calyceal fornix. Spontaneous resolution of hematuria can occur in childhood as the degree of renal vein compression improves, secondary to physical development and an increase in body mass index (*23*). Renal Doppler ultrasound can provide useful information on blood flow in the left renal vein and has been shown to be a useful non-invasive test in the diagnosis of nutcracker syndrome in children with hematuria (*24*).

HEMATURIA ORIGINATING FROM THE URINARY TRACT

There are a variety of causes of hematuria originating in the lower urinary tract, including infection, obstruction, and malignancies, as well as less well-understood entities such as loin-pain hematuria syndrome.

Idiopathic Hypercalciuria

Hypercalciuria is a common cause of both gross and microscopic hematuria in children. It is defined as a urinary calcium excretion greater than 4 mg/kg/day in a well child of any age, or a urine calcium/creatine ratio >0.2 in children older than 6 years of age. Most children are asymptomatic, although flank pain, dysuria, and urinary frequency on presentation have been reported. The pathogenesis of hematuria in the absence of stones is not well understood. However, many of these patients have a family history of urolithiasis, and a significant percentage of these patients may eventually develop stones themselves.

In a prospective, multi-center study of 215 patients with unexplained isolated hematuria, 76 patients (35%) overall were found to have hypercalciuria. Compared to patients with normal urinary calcium excretion, children with hematuria and hypercalciuria were characterized by male preponderance, Caucasian race, family history of urolithiasis, gross hematuria, and the presence of urine calcium oxalate crystals (*25*). Oral calcium loading tests in this population showed renal hypercalciuria in 26 patients (34%), absorptive hypercalciuria in 15 patients (20%), and were non-diagnostic in 35 patients (46%). Levels of serum parathyroid hormone, bicarbonate, phosphate, and urinary cAMP were similar in the three groups of hypercalciuric patients. During the follow up period, 13.3% of patients with hematuria and

hypercalciuria developed stones, compared to less than 0.1% of those with normal urinary calcium excretion.

Treatment of hypercalciuria is conservative, and consists of adequate fluid intake. Restriction of dietary calcium is not recommended as it may place these children at greater risk for bone demineralization. The use of thiazide diuretics to decrease urinary calcium excretion has been described but is only recommended for patients with intractable hematuria, a markedly increased urinary calcium-to-creatine ratio, and family history of urolithiasis (*26*).

Nephrolithiasis

The true incidence of renal stones among children in unknown. Estimates of the prevalence of nephrolithiasis are based on the number of hospital admissions related to renal stone and vary from 1 in 1000 to 1 in 7600, depending on the geographic region (*27*). Urinary calculi are found most often in Caucasian children and rarely in African American children. Boys and girls are affected equally. Symptoms of urolithiasis in children vary with age. Urinary tract infections are more common in preschool children with stones, while severe pain is encountered more often in adolescents. The finding of hematuria with urolithiasis, however, is relatively consistent throughout childhood, and either microscopic or macroscopic hematuria has been reported in 33–90% of children with stones (*27*).

As in adults, the study of choice for urinary imaging for detection of calculi is helical computed tomography without contrast. Treatment for urolithiasis depends on the stone burden. According to guidelines of the American Urologic Association, 98% of stones less than 5 mm in size pass spontaneously in adults. No comparative guidelines exist for the pediatric population. However, in a recent study by Van Savage et al., 55% of children with a distal ureteral stone measuring up to 3 mm passed the stone spontaneously. In contrast, stones larger than 4 mm were unlikely to pass spontaneously and required some form of surgical intervention (*28*). After passage or removal of the stone, prophylaxis depends on stone composition and metabolic abnormalities found on urine and serum studies.

Bacterial Infection

Urinary tract infections (UTIs), including pyelopnephritis, cystitis, and urethritis, are a common cause of gross or microscopic hematuria in children. UTIs occur in 3–5% of girls and 1% of boys, and are caused mainly by colonic bacteria. Hematuria associated with UTIs is typically accompanied by other symptoms, such as dysuria, frequency, fever, or abdominal pain. Urinalysis may reveal pyuria, bacteriuria, urinary nitrites, or leukocyte esterase. Suspected infections should be confirmed with a urine culture and treated according to bacterial sensitivities. Hematuria resolves as the associated inflammation of the urinary tract subsides.

Hemorrhagic Cystitis

Hemorrhagic cystitis is defined as acute or chronic bleeding of the bladder and is often associated with dysuria. Adenovirus, a common respiratory virus in children, causes hemorrhagic cystitis. Other etiologies include certain chemotherapeutic medications and radiation therapy. This complication occurs most often in immunocompromised transplant patients, but it can also affect healthy, normal children.

Obstruction

Ureteropelvic junction obstruction, often accompanied by hydronephrosis, occurs more commonly in boys than girls. The precise cause of UPJ obstruction remains elusive, but a number of intrinsic and extrinsic etiologies have been described. With the almost universal use of prenatal sonography, the majority of cases are identified and diagnosed in the perinatal period.

Beyond the perinatal period, urinary tract infection is the presenting sign in 30% of affected children. The older child may also present with episodic flank or abdominal pain, and cyclical nausea and vomiting. The sudden onset of gross hematuria is seen in approximately 25% of affected children, usually after minor abdominal trauma. The cause of hematuria is though to be due to disruption and rupture of mucosal vessels in the dilated collected system. Treatment of the obstruction, with subsequent resolution of hydronephrosis, also treats the hematuria.

Approximately 40% of children with UPJ obstruction also have associated vesicoureteral reflux (VUR). VUR can lead to hydronureteronephrosis, with secondary trauma to mucosal blood vessels. The etiology of hematuria in the setting of VUR is therefore similar to that in UPJ obstruction. As above, hematuria resolves with resolution of reflux and the accompanying urinary tract dilatation.

Urethrorrhagia

Urethrorrhagia typically presents as bloody spotting of the underwear in pre-pubertal boys. Approximately one-third of the cases are associated with dysuria. It is a self-limiting and benign disorder. Spontaneous resolution of symptoms occurs in over 90% of affected children over 2 years (*29*). Radiologic and laboratory evaluation has limited benefit. Endoscopic evaluation, if performed, only reveals bulbar urethral inflammation (Fig. 5.10) (*30*). Urethral manipulation in this population is controversial, as it is theorized to lead to stricture formation (*31*). Management of these patients is therefore expectant. Urethrorrhagia that persists beyond 2 years may be due to urethral stricture and warrants further evaluation with cystourethroscopy, retrograde urethrogram, or uroflometry.

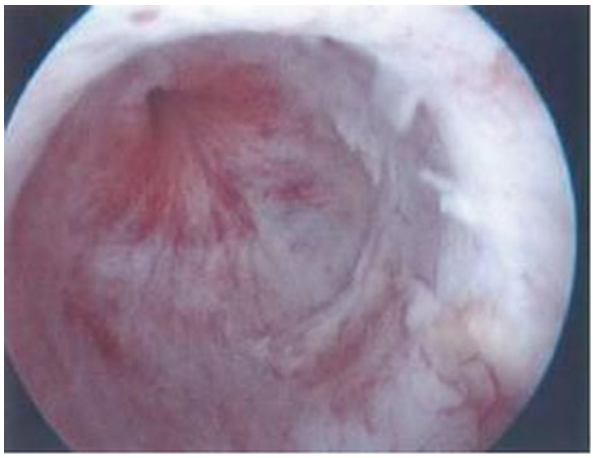


Fig. 5.10. Cystoscopy in a patient with urethrorrhagia reveals white membranous exudate at the bulbar urethra.

Heavy Exercise

Gross or microscopic hematuria can follow vigorous exercise. The urine may be red to black in color and may contain clots. Occasionally, heavy exercise may also lead to urine discoloration secondary to myoglobinuria. Urine culture is negative, renal ultrasound and VCUG are normal, and microscopic urinalysis does not reveal any evidence of red blood cell casts. Given the above characteristics, the source of bleeding is presumed to be the lower urinary tract. This is a benign condition. Hematuria is self-limiting and usually resolves within 48 h after cessation of exercise.

Loin Pain-Hematuria Syndrome

Loin pain-hematuria syndrome refers to episodes of unilateral or bilateral lumbar pain accompanied by microscopic or macroscopic hematuria. It is a diagnosis of exclusion, with an unclear etiology. Several authors consider this to be a psychopathologic disturbance, with similarities to Munchhausen syndrome by proxy.

EVALUATION

The basic evaluation of any child with hematuria begins with a detailed history and physical examination and may involve laboratory studies, radiologic studies, and tissue biopsies, depending on the presentation and associated symptoms. The evaluation of macroscopic or gross hematuria differs significantly from that of microscopic hematuria (Tables 5.5 and 5.6). As discussed previously, standard laboratory and imaging studies are of low yield and thus unnecessary in the setting of transient isolated microscopic

Table 5.5
Algorithm for management of microscopic hematuria

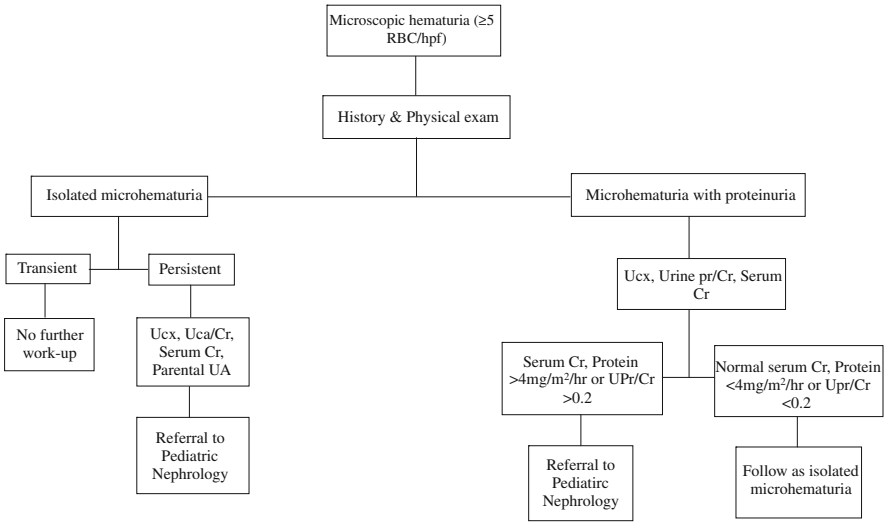
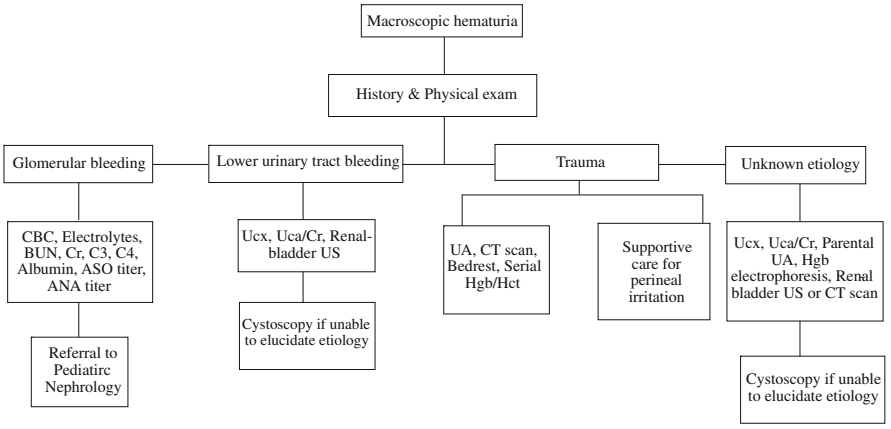

Microscopic hematuria (≥5 RBC/hpf)
History & Physical exam
Isolated microhematuria
Microhematuria with proteinuria
Transient
Persistent
No further work-up
Ucx, Uca/Cr, Serum Cr, Parental UA
Referral to Pediatric Nephrology
Ucx, Urine pr/Cr, Serum Cr
Serum Cr, Protein >4mg/m²/hr or UPr/Cr >0.2
Normal serum Cr, Protein <4mg/m²/hr or Upr/Cr <0.2
Referral to Pediatirc Nephrology
Follow as isolated microhematuria

Table 5.6
Algorithm for management of macroscopic hematuria


Macroscopic hematuria
History & Physical exam
Glomerular bleeding
Lower urinary tract bleeding
Trauma
Unknown etiology
CBC, Electrolytes, BUN, Cr, C3, C4, Albumin, ASO titer, ANA titer
Referral to Pediatirc Nephrology
Ucx, Uca/Cr, Renal-bladder US
Cystoscopy if unable to elucidate etiology
UA, CT scan, Bedrest, Serial Hgb/Hct
Supportive care for perineal irritation
Ucx, Uca/Cr, Parental UA, Hgb electrophoresis, Renal bladder US or CT scan
Cystoscopy if unable to elucidate etiology

hematuria, as most diagnoses in this category are benign. Children with persistent isolated microhematuria should be evaluated with a urine Ca/Cr ratio, parental urinalysis and Hgb electrophoresis, renal function tests, and possible renal-bladder ultrasound. If hematuria persists, they should be followed annually with renal function studies and blood pressure measurements to ensure that they do not develop hypertension or significant proteinuria. Extensive diagnostic evaluation should be reserved for children with gross hematuria, or microscopic hematuria with significant proteinuria or hypertension (*32*).

History

A detailed history of the patient's concurrent symptoms is key in identifying the etiology of hematuria (Table 5.7). Ascertaining whether pain accompanies hematuria is important; the presence of pain is uncharacteristic of glomerular diseases, and more suggestive of an infectious or obstructive process. The presence of irritative voiding symptoms with abdominal or flank pain suggests the possibility of a urinary tract infection or nephrolithiasis.

Table 5.7
History and physical examination findings

History
Abdominal, suprapubic, or costovertebral angle pain
Joint or muscle pain
Irritative voiding symptoms
Sore throat or skin infection
Systemic complaints – fever, nausea, vomiting, rash, arthralgia, cough, hemoptysis
Medications
Trauma
Exercise
Menstruation
Travel history
Family history
Hematuria
Deafness
Hypertension
Cystic kidney disease
Hemodialysis
Renal transplant
Coagulopathy or thrombocytopenia
Calculi
Physical examination
History
Edema
Nephromegaly
Costovertebral angle tenderness
Vertebral, anal and neurocutaneous abnormalities associated with malformation syndromes
External appearance of genitalia
Hypertension
Appearance of voided urine
Timing of hematuria in the urinary stream

Clues to glomerular disease include recent pharyngitis or streptococcal skin infections. Renal insufficiency should be suspected with reports of shortness of breath, edema, or weight gain from fluid retention. Symptoms of a systemic illness, such as rash, arthralgias, diarrhea, and hematochezia, can signal a vasculitis such as HSP, or a systemic illness such as SLE. Hemoptysis and cough may be seen in pulmonary-renal syndromes, such as Goodpasture's disease and Wegener's granulomatosis. The timing of hematuria, whether initial, constant, or terminal, may also help distinguish the site of bleeding in the urinary tract.

A variety of drugs and toxins can cause hematuria, hemoglobinuria, and rarely pigmenturia, and a medication history is, therefore, an important component of any comprehensive evaluation. Other pertinent personal medical history includes recent trauma, predisposing hematologic disorders, recent travel to tuberculosis or parasite-endemic areas, as well as the possibility of physical abuse.

A careful family history must also be obtained, with questions about hematuria, hearing loss, hypertension, nephrolithiasis, renal diseases, hemophilia, sickle cell disease, and dialysis or transplant. Answers to these questions can help identify patients at risk for Alport's syndrome, thin glomerular basement membrane disease, polycystic kidney disease, and hypercalciuria with or without urolithiasis.

Physical Examination

The physical examination should include assessment of height, weight and growth, to evaluate for chronic renal disease. General physical exam findings, such as pallor, fever, skin rashes, and musculoskeletal abnormalities are indicative of systemic diseases such as HSP and SLE. Edema is an important physical feature of nephrotic syndrome.

Malformation syndromes and genetic conditions associated with renal disease, such as VATER syndrome, tuberous sclerosis, and von Hippel Lindau disease, can present with a variety of physical findings, including vertebral, anal, and neurocutaneous abnormalities, and these entities can often be diagnosed based on physical findings alone. A thorough abdominal exam can assess for flank and abdominal tenderness, as well as abdominal masses due to tumor, hydronephrosis, or cystic renal disease. The presence of fever in the setting of costovertebral angle tenderness suggests an infectious process such as pyelonephritis. The genitalia should also be inspected for any signs of lacerations or bruising, caused either by accidents or abuse.

Blood pressure measurements should be performed to assess for hypertension, which can, in turn, be indicative of glomerulonephritis or renal insufficiency. In cases of severe hypertension, visual changes, epistaxis, and heart failure may be adjunct findings. The presence of hypertension is certainly an indication for a more rigorous evaluation of the underlying etiology of hematuria.

Physical appearance of the voided urine sample can provide further clues as to the possible source of hematuria. Macroscopic hematuria of glomerular origin is commonly brown, tea-colored, or cola-colored, whereas gross hematuria from the lower urinary tract is usually pink or red.

Laboratory Testing

The laboratory evaluation begins with a urinalysis and urine culture, to rule out the possibility of a urinary tract infection. Proteinuria and red blood cell casts are markers of glomerular disease and initial urinalysis should include urine microscopy to determine the presence of RBC casts. Proteinuria is best assessed with a 24-h urine collection or with a first morning urine protein/creatinine ratio, in order to eliminate the possibility of orthostatic proteinuria. Urine protein excretion ≤ 4 g/m^2/hr, or urine protein/creatinine ratio <0.5 in children below 2 years of age and <0.2 in children above 2 years of age, suggests normal protein excretion. The presence of proteinuria in excess of these values necessitates further evaluation. Nephrotic range proteinuria is defined as urine protein >40 g/m^2/hr or protein/Cr ratio >3.

The work-up of glomerular causes of hematuria consists of a complete blood count, serum C3 and C4 concentration, serum BUN, creatinine, and potassium levels. In the appropriate clinical setting, evaluation for recent streptococcal infection, either with a throat culture or ASO titers is also indicated. If nephrotic syndrome is suspected, based on degree of proteinuria or edema, serum albumin should also be measured. Systemic illnesses, such as SLE as well as various vasculitides can, when present, be the sole etiology of hematuria. Children with signs and symptoms suggestive of a systemic vasculitis and with a family history significant for such illnesses should be additionally screened with ANA, pANCA, cANCA, dsDNA, and anti-GBM titers.

All children with hematuria should undergo hematologic studies to eliminate the possibility of underlying disorders such as sickle cell nephropathy, coagulopathy, or thrombocytopenia if history or physical examination is suggestive. Hypercalciuria, with or without nephrolithiasis, is a common etiology that should also be investigated in all children with hematuria, either with a 24-h urine calcium or a spot urine calcium/creatinine (Ca/Cr) ratio. Significant hypercalciuria, defined as 24-h urinary calcium excretion >4 mg/kg, or a Ca/Cr ratio >0.2, is an indication for radiologic evaluation for stone disease.

Radiologic Testing

Ultrasound and computed tomography remain the most commonly used imaging modalities in the work-up of hematuria in children. Macroscopic hematuria in the absence of significant proteinuria or red blood cell casts is an indication for a renal-bladder ultrasound to exclude malignancy or cystic kidney disease. Ultrasound is also indicated for the evaluation of

hydronephrosis, secondary to UPJ obstruction or vesicoureteral reflux, as a possible cause of hematuria. Vascular causes of hematuria, such as thrombosis of the renal artery and vein, or the nutcracker syndrome, are best evaluated by renal Doppler ultrasound.

While ultrasound and abdominal X-rays are used in the work-up of stone disease, non-contrast CT scan remains the gold standard for the detection and most accurate size estimate of renal and ureteral calculi. As previously discussed, CT imaging with and without contrast enhancement also plays a central role in the evaluation of gross or microscopic hematuria secondary to trauma.

Radiologic testing is not routinely recommended for the evaluation of glomerular causes of hematuria, but diminishing renal function in the setting of glomerular disease should be evaluated by imaging to rule out any additional abnormalities.

Biopsy

Renal biopsy is the only definitive means of diagnosing and distinguishing between glomerular causes of hematuria, with the exception of acute post-streptococcal glomerulonephritis (PSGN), which can often be diagnosed on the basis of history and symptom course alone. However, renal biopsy should be performed for PSGN if gross hematuria, proteinuria, hypocomplementemia, and diminished renal function do not spontaneously improve within 2 months after onset or in the face of a rapidly rising creatinine to rule out crescentic glomerulonephrits. Persistent or worsening hypertension in the setting of microscopic or macroscopic hematuria can be a sign of progressive renal damage, requiring further evaluation by renal biopsy. Although not indicated, parental anxiety may also drive the performance of a renal biopsy for children with persistent isolated microhematuria.

Cystoscopy

The yield of cystoscopy is the evaluation of hematuria in children is low. Furthermore, because of the invasive nature of this test, and the need for general anesthesia in many pediatric patients, cystoscopic evaluation is not routinely recommended. If a complete work-up including laboratory analysis and radiologic testing has yielded minimal or conflicting data as to the etiology of hematuria, cystoscopy is advised to rule out bladder pathology. Naturally, cystoscopy is also indicated when imaging studies raise the possibility of a bladder mass, albeit rare in the pediatric population.

Occasionally, hematuria may be result of urethral trauma or bladder outlet obstruction secondary to posterior urethral valves, and cystoscopy may help differentiate between these possibilities. Cystoscopy may also be used to lateralize bleeding from the upper tract, but its utility is limited to episodes of active bleeding.

Referral

Referral to a urologist is indicated when the work-up is suggestive of an anatomic abnormality, tumor, calculus, or recurrent macroscopic hematuria of undetermined origin. Urologic referral is also required in cases of trauma to the genitourinary tract. In contrast, the presence of hematuria in association with hypertension, proteinuria, hypocomplementemia, systemic disease, or a family history of glomerulonephritis or renal disease almost always warrants referral to a nephrologist rather than a urologist.

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REFERENCES

1. Moore GP and Robinson M. Do urine dipsticks reliably predict microhematuria? The bloody truth! Annals of Emergency Medicine 1988; 17(3):257–60.
2. Davis ID and Avner ED. Clinical evaluation of the child with hematuria. In: Kleigman RM et al. (eds). Nelson textbook of Pediatrics, 18th ed. Saunders Elsevier, Philadelphia, 2007; 2168–2188.
3. Lee YM, Baek SY et al. Analysis of renal biopsies performed in children with abnormal findings in urinary mass screening. Acta Paediatrica 2006; 95(7):772–773.
4. Hisano S and Ueda K. Asymptomatic haematuria and proteinuria: renal pathology and clinical outcome in 54 children. Pediatric Nephrology 1989; 3(3):229–234.
5. Noe HN and Jones DP. Renal Diseases in Childhood. In: Wein AJ et al. (eds). Campbell-Walsh Urology, 9th ed. Saunders Elsevier, Philadelphia, 2007; 3217–3231.
6. Vehaskari VM, Rapola J, et al. Microscopic hematuria in school children: epidemiology and clinicopathologic evaluation. Journal of Pediatrics 1979; 95:676–684.
7. Hisano S, Kwano M et al. Asymptomatic microhaematuria: natural history of 136 children. Pediatric Nephrology 1991; 5(5):578–581.
8. Feld LG, Meyers KE et al. Limited evaluation of microscopic hematuria in pediatrics. Pediatrics 1998; 102(4):E42.
9. Ingelfinger JR, Davis AE et al. Frequency and etiology of gross hematuria in a general pediatric setting. Pediatrics 1997; 59(4):557–561.
10. Greenfield SP, Williot P et al. Gross hematuria in children: A ten year review. Journal of Urology 2007; 69(1):166–169.
11. Youn T, Trachtman H, et al. Clinical spectrum of gross hematuria in pediatric patients. Clinical Pediatrics 2006; 45:135–141.
12. Gharavi AG, Yan Y et al. IgA nephropathy, the most common cause of glomerulonephritis, is linked to 6q22-23. Nature Genetics 2000; 26:354–357.
13. Patel HP and Bissler JJ. Hematuria in children. Pediatric Clinics of North America 2001; 48(6):1519–1537.
14. Hisano S, Kwano et al. The natural history of screening detected IgA glomerulonephritis in children. Acta Paediatric Scandanaica 1991; 80:1044–1050.
15. Badenas C, Praga M et al. Mutations in the COL4A4 and COL4A3 genes cause benign familial hematuria. Journal of the American Society of Nephrology 2002; 13(4): 1248–1254.
16. Ronnefarth G, Misselwitz et al. Nephrocalcinosis in children: a retrospective survery. Pediatric Nephrology 2000; 14:1016–1021.

17. Buckley JC and McAninch JW. The diagnosis, management, and outcomes of pediatric renal injuries. Urologic Clinics of North America 2006; 33:33–40.
18. Brown SL, Elder JS, et al. Are pediatric patients more susceptible to major renal injury from blunt trauma? A comparative study. Journal of Urology 1998; 160:138–140.
19. Buckley JC, McAninch JW. Pediatric renal injuries: management guidelines from a 25-year experience. Journal of Urology 2004; 172(2):687–690.
20. Tarry WF, Duckett JW et al. Urologic complications of sickle cell disease in a pediatric population. Journal of Urology 1987; 138:592–594.
21. Peters CA. Perinatal Urology. In: Wein AJ et al. (eds). Campbell-Walsh Urology, 9th ed. Saunders Elsevier, Philadelphia, 2007; 3176–3197.
22. Kavaler E and Hensle TW. Renal artery thrombosis in the newborn infant. Urology 1997; 50(2):282–284.
23. Shin JI, Park JM et al. Factors affecting spontaneous resolution of hematuria in childhood nutcracker syndrome. Pediatric Nephrology 2005; 20:609–613.
24. Shin JL, Park JM et al. Doppler ultrasonographic indices in diagnosing nutcracker syndrome in children. Pediatric Nephrology 2007; 22:409–413.
25. Stapleton FB. Idiopathic hypercalciuria: association with isolated hematuria and risk for urolithiasis in children. The Southwest Pediatric Nephrology Study Group. Kidney International 1990; 37(2):807–811.
26. Parekh DJ, Pope JC et al. The association of an increased urinary calcium-to-creatinine ratio, and asymptomatic gross and microscopic hematuria in children. Journal of Urology 2002; 167(1):272–274.
27. Stapleton FB. Childhood stones. Endocrinology and Metabolism Clinics 2002; 31(4):1001–1015.
28. Van Savage JG, Palanca LG et al. Treatment of distal ureteral stones in children: similarities to the American Urological Association guidelines in adults. Journal of Urology 2000; 164(3):1089–1093.
29. Walker BR, Ellison ED et al. The natural history of idiopathic urethrorrhagia in boys. Journal of Urology 2001; 166(1):232–233.
30. Meyers KEC. Evaluation of hematuria in children. Urologic Clinics of North America 2004; 31:559–573.
31. Poch MA, Handel LN et al. The association of urethrorrhagia and urethral stricture disease. Journal of Pediatric Urology 2007; 3:218–222.
32. Pan CG. Evaluation of gross hematuria. Pediatric Clinics of North America 2206; 53:401–412.

6 Office Procedures

Patrick C. Cartwright and M. Chad Wallis

Abstract The performance of minor procedures in a pediatric urology office setting can be attractive to families and provide high-quality outcomes in a cost-effective manner. An optimal office environment and supportive approach with the family and child are crucial to success. Procedures including standard newborn circumcision, sutured circumcision, catheterization, the teaching of intermittent catheterization, urethral meatotomy, lysis of penile or labial adhesions, placement of suprapubic catheter, and the manipulation of various stents and catheters may all be accomplished very appropriately in an office setting. Having the office fully prepared for such procedures and providing pre-emptive explanations and care handouts to the patient and the family are the key.

Keywords Pediatric urology · Office procedures · Circumcision · Meatotomy · Urethral catheterization

INTRODUCTION

The ability to perform office procedures in the pediatric population maintains an appeal to both parents and physicians for a variety of reasons. It generally allows the parents to be present during the procedure, which can be helpful in providing comfort to the patient. A high level of satisfaction has been demonstrated among parents who elect to have procedures done in the office setting (*1*). It frees up operating room time which comes at a premium in most practices. Finally, it is more cost effective and eliminates the risk of general anesthesia.

As with all surgical procedures, patient selection is an important component of the process when deciding whether to perform a procedure in the office or in a more acute setting such as in the operating room or an anesthesia satellite clinic using either general anesthesia or some form of sedation. Newborns and infants with no significant co-morbidities are good

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candidates. Toddlers and school-age children usually require more physician discretion. Observing the patient during the initial examination is an important part of patient selection. We have found that patients who lay still and are comfortable with being examined typically do very well for those procedures that require only a topical anesthetic. Those patients who are unable to remain still for an examination or have a significant amount of anxiety may be better candidates to have the procedure performed with some sedation or under general anesthesia. We have found that hospital-based sedation areas have been an excellent setting for these patients.

THE PEDIATRIC UROLOGY OFFICE

The surroundings in a medical office should serve to make children and their parents comfortable. Distractions such as books, toys, and puzzles can help keep children at ease and help reduce anxiety levels. Having one room that is dedicated for procedures is often ideal so that it does not slow down the flow of other patients. This room should have adequate lighting and be large enough to accommodate parents and office staff needed to assist with making the child comfortable during the procedure. A basic tray of surgical instruments will take care of the most commonly performed office procedures. This should include a needle driver, scissors, fine hemostats and forceps, and a knife handle. A papoose board is also important for helping restrain infants during procedures. For infants that are too large for a papoose board, a sandbag may be placed over the legs to keep them still during the procedure.

PAIN/ANXIETY MANAGEMENT

Evidence of increased sensitivity to pain in neonates compared to older children and adults should put to rest the notion that infants do not feel pain (*2*). The American Academy of Pediatrics has indicated that all boys who undergo neonatal circumcision should be given appropriate analgesia (*3*). Consideration should be given to appropriate pain management in all children and infants who undergo any type of procedure in the office setting.

Procedures on the penis are the most common in a pediatric urology office. Patients undergoing circumcision in the office setting will generally do best with an injectable local anesthetic. A recent Cochrane review of pain management during circumcision identified the dorsal penile nerve block (DPNB) as the most effective intervention for pain management during neonatal circumcisions (*4*). The dorsal nerves of the penis are terminal branches of the pudendal nerve and innervate all but the most proximal part of the penis. The subpubic approach is generally considered the safest approach to these nerves. As the blood supply to the penis comes from terminal arteries, some of which run alongside the dorsal nerves, use of

epinephrine containing local anesthetics is contraindicated when performing a DPNB. We typically will perform a DPNB as well as a ring block at the base of the penis and have found this to be very effective. Both lidocaine and bupivacaine are the most commonly used local anesthetics. The dosage of lidocaine should not exceed 5 mg/kg and a dosage of bupivacaine should not exceed 2.5 mg/kg. We tend to use a mixture of 0.25% bupivacaine and 0.5% lidocaine to provide effective short-term and long-term analgesia.

As indicated previously, proper patient selection is important to ensure satisfied parents and patients. Toddlers and older children who are deemed to be good candidates for an office procedure will typically do best if injections are avoided and a topical anesthetic alone is used. A eutectic mixture of topical anesthetics (EMLA; lidocaine and prilocaine) has been very successful in our practice for minor procedures such as lysis of penile adhesions and meatotomy in this patient population (*5*). The EMLA cream is placed on the penis and secured with an occlusive dressing (Tegaderm). The patient's parents should be informed that application of the EMLA cream requires a 1-h waiting period for optimal analgesic effect. This will allow them to bring their own games and activities from home to occupy the child's time as well as their own during the waiting period. We find that many families choose to bring in DVD players to watch movies during this time. Once the appropriate time has elapsed, the occlusive dressing can be removed and the EMLA cream wiped off. The analgesia typically lasts for 1–2 h after the cream is removed. These topical creams are associated with few complications and are well tolerated in the vast majority of patients. The prilocaine component of the EMLA cream poses a small but documented risk of methemoglobinemia. Infants younger than 3 months of age are at higher risk for this uncommon event because they have lower levels of Met-Hgb reductase than older children and adults (*6*).

If significant anxiety is anticipated from a particular patient or due to the nature of a procedure, oral sedation (usually midazolam) can be achieved in the office if appropriate resuscitation equipment is available. In our practice we choose to do intravenous sedation (usually propofol) in a hospital-based sedation area.

Patient and parent positioning can also be helpful in providing comfort and distraction to ease the anxiety of a potentially painful procedure. For the vast majority of procedures, the supine position is most appropriate. In girls, placing the heels together with the knees bent and then allowing the legs to fall down laterally in a frog-leg position facilitates access to the introitus. We find it helpful to have the child hold a book on his or her abdomen as a pseudo "ether screen." If a parent or caregiver sits at the head of the bed they can read to the patient and point out pictures in the book. This serves as a distraction to prevent the child from becoming preoccupied with the procedure and to give the child something to hold, thus preventing contamination of the surgical field (Fig. 6.1).

Fig. 6.1. Patient positioning. With a parent positioned at the head of the bed, a colorful book can be used to help distract a child, keep their hands occupied and block their view of the procedure to reduce anxiety.

PENILE PROCEDURES

Circumcision

Neonatal circumcisions are typically performed in the first 1–2 weeks of life. Depending on the community they are performed by either pediatricians or obstetricians. Patients referred to a pediatric urology practice often have an abnormality of the penis that made the primary physician uncomfortable with performing a neonatal circumcision. Other patients may have had the circumcision delayed for any number of reasons to the point that the child is beyond the age at which the primary physician is willing to perform an office circumcision. Jayanthi et al. demonstrated that an office circumcision can even be performed in children over 3 months of age in a pediatric urology office setting (7). They also demonstrated significant cost reduction for both the patients and the healthcare system by performing these procedures in the office as opposed to doing them in the operating room. In addition, this may help free up valuable operating room time for the practicing urologist.

There are a variety of techniques for performing a neonatal circumcision. The Gomco clamp and Plastibell are perhaps the most commonly used techniques. A Mogen clamp may also be used. Alternatively we have found that a free-hand circumcision can be performed in the office setting without much difficulty. The free-hand technique is often helpful for patients who have been referred because they have an incomplete foreskin and therefore are not amenable to having a circumcision performed by one of the other techniques. All these techniques have potential for complications. Ultimately the

physician must be responsible for choosing the technique with which he or she feels most comfortable and has the greatest amount of experience.

Contraindications to performing a circumcision in the office would include any urethral abnormalities such as hypospadias, epispadias, or megaurethra as well as any abnormalities of the corpora such as penile curvature and significant penile torsion. Patients with large hydroceles or hernias are more likely to have complications with secondary phimosis or a concealed penis. In addition, performing a neonatal circumcision on a patient with penoscrotal webbing may also lead to a concealed or even entrapped penis.

The Gomco, Plastibell, and Mogen clamp devices all rely on compression for hemostasis. The most common problem in the immediate post-procedure period is bleeding. In patients who have undergone a Plastibell circumcision the Plastibell must be removed in order to identify the area of bleeding and in order to apply direct pressure. Once this has been done, the bleeding is typically easily controlled with suture ligation. Removal of the Plastibell generally requires suturing of the entire circumference of the penile skin when it occurs relatively soon after the procedure is performed. Direct pressure may be used to control bleeding following a circumcision by any of the other techniques. In addition, some have used surgical cellulose (Surgicel), topical thrombin, and dilute epinephrine-soaked sponges. The adjunct to these is a modestly compressive bandage; an inner layer of Telfa wrapped with Coban or Conform is generally adequate. If these are ineffective, then identification of the bleeding vessel and suture ligation is necessary. Other complications include infection, penile adhesions, secondary phimosis, and meatal stenosis. More dramatic complications such as glans amputation or penile necrosis are rare. Complication rates vary from 0.2–3% for neonatal circumcision (*8*).

Penile Adhesions

Penile adhesions may be either physiologic or pathologic. Generally these adhesions occur between the glans and the inner preputial skin when this has not been taken down appropriately. When the foreskin is retracted, if the edges of these adhesions are thin, then a steroid cream can be utilized to help promote lysis with a good success rate. Betamethasone 0.05% is the most commonly used steroid agent for physiologic adhesions. The skin is retracted and the cream is applied to the adhesions 2–3 times a day for a period of 3–5 weeks with success rates of 67–95% (*9*). If, however, there are dense adhesions and the skin is actually fused to the glans, these will not respond to steroid treatment and require surgical lysis.

Lysis can be performed in the office using EMLA, which is applied to the penis followed by an occlusive dressing as indicated previously. Placing some of the EMLA cream beneath the skin bridge can be achieved using a small syringe and a 22 IV plastic cannula (no needle). After leaving the

EMLA cream in place for over 60 min the dressing should be removed and the cream wiped off. The skin bridge is prepped in a sterile fashion and then a hemostat can be applied across the bridge to provide hemostasis. The hemostat is removed and the skin bridge can be incised. Generally no sutures are needed. If there are extensive adhesions, use of some fine absorbable sutures may be necessary. A petroleum-based ointment, such as Vaseline, should then be applied 2–3 times per day for at least 2 weeks to prevent reattachment.

Meatotomy

Meatotomy for correction of meatal stenosis is perhaps the most commonly performed pediatric urology office procedure. This procedure is also well suited to analgesia with EMLA cream. After applying the cream and waiting the requisite 1-h time period, the penis is wiped free of EMLA. The skin is then prepped and the ventral skin overlying the meatus is crushed with a straight hemostat. Curved Iris scissors can then be used to incise the stenotic portion of the meatus. When done properly, there is typically no bleeding and no need for suturing. We then find it helpful to demonstrate for the parents how to apply Vaseline ointment within the meatus to prevent the edges from healing back together, causing recurrence of the stenosis. The parents are instructed to apply this regularly for several weeks.

Morbidity from this procedure is minimal. There is typically mild dysuria for the first 24–48 h following the procedure. This may result in voluntary urinary retention in smaller children that is best managed with continued observation and warm sitz baths. There may also be some erythema and induration of the meatus; however, this typically subsides within a few days.

Paraphimosis

Boys will occasionally present to the office with paraphimosis due either to manipulation from medical personnel, or occasionally from self-retraction of the foreskin without knowing that it must be pushed back distally again after retraction. If the duration of paraphimosis is relatively short and the edema of the foreskin minimal, this can be gently reduced in the office without much difficulty. The technique is similar to adults where thumbs push the glans proximally as the index and middle fingers of each hand simultaneously draw the swollen prepuce distally. It will often take 2–3 min of gentle pressure until the foreskin slides back into normal position. If the patient is unable to tolerate this then either oral or IV sedation will be required. Particularly tight and edematous paraphimosis may require deep sedation or even general anesthesia for management. Once reduced, the amount of edema in the foreskin can be rather dramatic but resolves promptly.

PROCEDURES ON THE FEMALE GENITALIA

Lysis of Labial Adhesions

Labial adhesions occur in approximately 1–3% of prepubertal girls. This most commonly occurs between 1 and 2 years of age (*10*). Although the exact etiology is unknown, it may be related to lower estrogen levels in prepubertal children. Edges of the labia minora may become denuded due to local irritation. Contact between the edges would then cause re-epithelialization and fusion in the mid-line. Children are typically asymptomatic but may have vaginal irritation, urinary tract infections, dysuria, or even post-void dribbling due to vaginal reflux of urine.

Treatment is typically performed locally with topical application of conjugated estrogen (Premarin) cream. This can be applied to the area of the adhesions with a cotton swab twice per day for up to 2 weeks. We prefer not to treat the adhesions for longer than this. Even during a short course of 2 weeks, side effects of breast budding and labial engorgement may occur. These typically resolve when the cream is discontinued. Myers et al. recently reported the use of betamethasone 0.05% cream with similar success rates to those of estrogen cream and without any hormone-related side effects (*11*). If symptoms persist and topical estrogen therapy or use of betamethasone is not effective, then surgical lysis of the adhesions is performed. We have used EMLA cream as a topical anesthetic under an occlusive dressing and found that this allows for modest (usually not complete) local anesthesia. The adhesion is then easily separated with either a cotton swab or sterile probe. Thicker adhesions may require a hemostat to spread the adhesion. Postoperatively we have applied Vaseline to the area 2–3 times per day for 2–3 weeks to allow for healing without re-epithelialization and fusion.

Prolapsing Ureterocele/Imperforate Hymen

On rare occasion, a young girl will present to the office with an acute onset introital mass. There are key circumstances in which a small procedure may be considered in the office. First, in the case of prolapsing ureterocele, this will often serve an obstructed and infected upper pole ureter. If a suspicious mass is seen coming from the urethra, ureterocele should be suspected. Ureteroceles will be visualized only intermittently at the introitus as they prolapse. When it is visible a small suture may be placed into it, thus keeping it out until incision can be accomplished. The small incision may then be made in the ureterocele wall to drain infected urine. This will allow the ureterocele to collapse and it can then be allowed to retract. Optimally, once the ureterocele is visualized and secured, an ultrasound is obtained before incision is completed. This gives maximal anatomic definition before drainage.

The other situation similar (but not intermittent) to this will be imperforate hymen with bulging intravaginal fluid behind this or hydrometrocolpos

from another anatomic problem such as a duplex vagina with obstruction. In these circumstances, ultrasound is again first obtained but then office drainage with simple incision may be appropriate.

MISCELLANEOUS PROCEDURES

Urethral Catheterization

Avoiding catheterization in children whenever possible is best, but at times will be necessary. Most commonly, this will be performed to obtain a sterile sample for culture. While the majority of catheterizations will be simple, challenging patients or circumstances may require alternative approaches to be successful.

A key with any child is preparing them as best as possible for what is to come. A very simple explanation is the starting point, always assuring them that you will listen to anything they want to tell you. Explain that you will be soft but that they will feel the tube passing through the urethra, that it will be an uncomfortable sensation, and they may have an urge to void. As the catheter is being passed, continual reassurance with direct eye contact (especially in infant and young children) and listening will let them know that you are plugged into their feelings; this will go a long way.

The supine position is simplest. Topical Betadine prep and a non-latex straight urethral catheter are most appropriate when obtaining a sample for culture. Water-soluble lubricant on the tip of the catheter is often enough to avoid any friction in the urethra during passage. For children less than six months of age, it is appropriate to try an 8-Fr catheter. This may prove too large (especially in premature boys) and switching to a 5-Fr feeding tube may be best. With older children, it is best to have a parent hold their child's shoulders and arms gently while reassuring the child face to face during the procedure. A second assistant may need to hold legs; this is best done with the assistant positioned at the foot of the bed reaching up and securing the legs mid-way between knee and hip so that the hold is secure. Even young children can be a challenge to restrain and some strength from the foot-side assistant is needed.

For girls, the simplest technique for catheter passage is separation of the labia with the fingers of one hand for direct visualization of the meatus and placement of the catheter with the other hand. The meatus can be quite small and hidden by redundant tissue just anterior to the vaginal introitus. Once the catheter enters the urethra it should be advanced slowly and gently; within 3 cm the tip of the catheter has entered the bladder. If the catheter is to be retained for a VCUG or other study, it can be passed approximately 8 cm and then secured just outside the labia with tape. The most common catheterization challenge in girls is a urethral meatus which faces slightly posteriorly or is just inside the introitus and cannot be visualized easily. In this circumstance, the hand used to separate the labia may be drawn anteriorly once

the labia are separated; this tends to roll the urethra and surrounding tissues slightly upward and into view.

If the meatus still cannot be visualized, certain adjuncts may help with catheter placement. With each of these approaches, the tip of the catheter should be kept in the exact mid-line and directed anteriorly as it slips just under the anterior edge of the vagina. Even if the meatus can not be visualized, the engagement of the catheter tip can be clearly felt. First, using a straight catheter, the angle of approach can be adjusted such that the catheter tip advances more anteriorly rather than straight in. This requires placing the hand that is advancing the catheter more posteriorly (against the table), thus allowing the tip to be directed anteriorly. If this is unsuccessful, a coudé tip catheter (8 Fr or larger) may be used with the bend facing anteriorly. Finally, a feeding tube or straight catheter may be adjusted to a variable bend by using a small lacrimal duct probe placed into the distal eyelet of the catheter and bent to the desired angle. Once the tip of the catheter has entered the meatus the catheter is advanced forward off the lacrimal duct probe to complete passage into the bladder (Fig. 6.2).

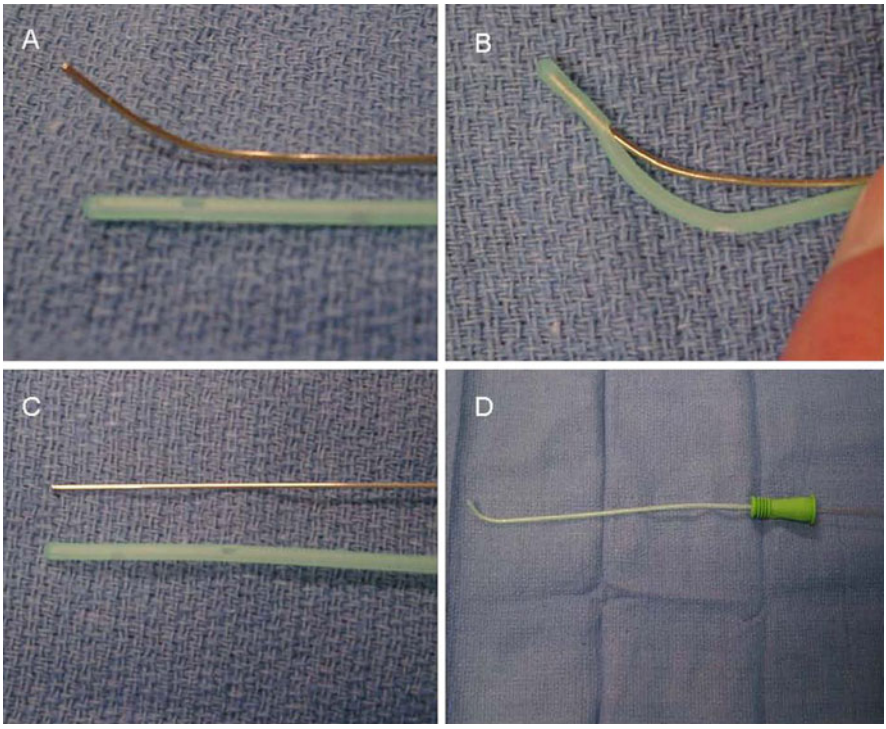

Fig. 6.2. Urethral catheterization. A lacrimal duct probe (**a**) can be useful in catheterizing girls to create a small bend in the tip of the catheter (**b**). Using 22-guage stainless steel wire (**c**), a stylet can be created for catheters as small as 8 Fr (**d**) to aid in catheterizing boys.

Different challenges in catheterization are encountered in boys. If circumcised, simple catheterization with a lubricated straight catheter is appropriate. Resistance may be encountered at the external sphincter and this is best managed with mild pressure of the catheter tip against the sphincter for a short period until the muscle fatigues and the catheter passes. For most boys under one year of age, it will be 8–10 cm from the urethral meatus until the tip of the catheter has passed into the bladder.

Male urinary tract abnormalities may require added measures for catheterization. With unrepaired hypospadias, the urethral meatus will be at some location along the ventrum of the penis. If catheterization is required, looking for the most proximal opening along the shaft is key. Distal to the true hypospadiac meatus there may be urethral pits or other meatus-like structures which can be confusing. Always select the most proximal of the openings to find the actual urethral channel. If the catheter is only passing 1–2 cm in these circumstances, then it is likely that the tip has entered a secondary urethral pit and not the true lumen. Additionally, it can clearly be difficult to catheterize a patient with a prior hypospadias repair. If there is stricture or stenosis of the repair, this is likely to require surgical revision. More commonly, the catheter will enter the repaired segment of the urethra and not advance easily due to irregularity or redundancy of the lumen. The best approach for these patients is to use the off hand to compress the urethra around the catheter tip (a coudé tip may be helpful) so that it hugs the dorsal aspect of the urethra (against the corpora) while passage is attempted. This often guides the tip of the catheter through the smoothest part of the repair and into the normal proximal urethra.

Other male urethral catheterization challenges may be encountered. False passages in the bulbar urethra arise in boys on intermittent catheterization or even following a single traumatic catheterization. A coudé tip catheter is generally the best approach in this circumstance with the tip again directed anteriorly (toward the corpora cavernosa). Perineal pressure may be required under the inferior arch of the pubis to direct the catheter anteriorly rather than the tip finding its way into the usual posterior false passage. Patients with a posterior urethral valve may also present a special catheterization challenge. At diagnosis, most patients with a valve can be catheterized in a retrograde fashion as the valve easily pushes aside. However, once past the valve and into the prostatic urethra, the tip of the catheter will often not easily traverse the bladder neck. This is secondary to a capacious prostatic fossa and prominent bladder neck associated with the obstruction. This is similar to a post-TURP prostatic fossa in an adult. In these patients, the first thing to try is a coudé tipped catheter directed anteriorly. Next, a catheter can be passed while the little finger is placed in the rectum and the prostatic fossa is compressed anteriorly. The final adjunct, which should be used cautiously, is to place a lubricated 22-G stainless steel wire (used mostly for sternal closures) within the lumen of the catheter and use it as a catheter stylet. This will allow for variable bending of the tip and often allow passage over

the bladder neck. As with any catheter on a stylet, once in the bladder the catheter is advanced off the stylet carefully. This stylet approach may be used with either a straight or Foley catheter. The 22-G stainless steel wire works as a make-shift stylet with catheters down to 8 Fr size (Fig. 6.2).

Yet another challenge in catheterization is the boy with non-retractile foreskin. The penis may be prepped externally and a small catheter placed through the preputial aperture with thumb and finger of the off hand holding the glans. The catheter can be steered to the mid-line and often, even without visualization, will pass into the meatus. In this scenario, only the outer prepuce is prepped, and obtaining a sterile sample is not possible. If sterile urine is needed, then placing Betadine under the preputial aperture by instilling a small amount through a 22-G IV cannula (no needle), which has been placed into this space between prepuce and glans is needed. This will provide some degree of inner preputial prep and catheterization can then be carried out. Otherwise, suprapubic aspiration will be required to obtain a specimen adequate for culture.

Anytime a challenging catheterization is anticipated, it is wise to first place 5 ml of 2% lidocaine gel within the urethra. In older boys this can be done with the standard dispenser tip on the lidocaine gel syringe. However, for a younger boy, the tip is too large; a useful maneuver is to squirt the lidocaine gel into a 5 or 10 ml syringe and then place a 20- or 22-G IV canula (no needle) on the syringe. This canula can then be inserted into the meatus and the lidocaine gel instilled. Leaving the gel in place for at least 5 min before passing the catheter is best. In the particularly challenging patient, it may be appropriate to use oral sedation (usually midazolam) prior to catheterization. The other adjunct is to take the patient to a radiographic suite where retrograde urethral contrast (or contrast mixed with lidocaine gel) injection may help find the problem area and then allow visualization of the catheter tip in real time during passage. The final consideration in catheterizing children with complex anomalies is to use oral prophylactic antibiotics given within an hour before catheterization.

In boys following a hypospadias repair or occasionally in other conditions, only meatal dilation or calibration is required and not full urethral catheterization. This can be done with a lubricated tip from a regular catheter and the parents can be taught to do this at home. Alternatively, small tubes of ophthalmic ointment (such as Lacri-Lube) have an appropriately small metal tip which is approximately 6 Fr distally and 8 Fr proximally; and is about 1 cm in length. The ophthalmic ointment can be used as the lubricant and this metal tip then becomes an ideal home dilator for parents to use in case of meatal narrowing.

Teaching Clean Intermittent Catheterization

Many children with neurogenic bladder will require clean intermittent catheterization. This is best taught in the office setting with an experienced

clinician or nurse. At least 45 min should be set aside for appropriate education of child and parent and the technique can then be taught to as many family members as possible so all can assist with catheterization.

Generally, parents will learn to catheterize first after the physician or nurse demonstrates the technique. Once the parent is comfortable with this then the child may be taught, as desired. The crucial elements in teaching involve clean technique (including management of catheters, washing of hands, topical antiseptic before catheterization), locating the meatus (a mirror may help), and positioning for the catheterization with appropriate collection and drainage of urine without soiling the patient.

Catheterizing in a supine position may be simplest for some patients but this may also be a difficult position to get into in many settings. Working with children sitting on the toilet to both identify the urethra and be in a stable upper body position where they can reproducibly catheterize requires experienced nurses, physical therapists, and occupational therapists to achieve. Ideally, a multidisciplinary catheterization clinic associated with a pediatric hospital can assist in this process.

Suprapubic Access to the Bladder

In neonates with a febrile illness where urinary tract infection is suspected, suprapubic aspiration may be the most appropriate way to acquire urine. Certainly this is the method that is least prone to contamination. As previously mentioned, uncircumcised boys may require suprapubic aspiration to obtain a sterile sample for culture.

The bladder is first palpated for some degree of fullness. An area 1 cm above the pubis in the mid-line is prepped and anesthetized with 1% lidocaine down to fascia. A 1¼ inch 25-G needle is next connected to a 10 cc syringe and while gently aspirating, the needle is advanced with the tip directed slightly superiorly from the insertion site. Once urine is obtained, the syringe is filled and the needle removed. If no urine is obtained with passage then the patient should be hydrated and the aspiration attempted again after 30–60 min. An alternative approach is to use sonographic imaging to determine the bladder fullness and depth from skin. If ultrasound is available in the office, this approach is favored.

In unusual circumstances, placement of a percutaneous suprapubic catheter can be required in the office. This may be done with or without sedation by again anesthetizing skin and localizing the bladder with the same 25-G needle. Prepackaged suprapubic kits with an 8-Fr tube may be used. For younger children an alternative is to use a 14-gauge IV cannula as the introducing trocar through which a 5-French feeding tube can be advanced into the bladder (Fig. 6.3). The cannula is then backed off the feeding tube and the tube is secured in some manner. This technique may be quite useful in hospitalized patients (especially NICU) needing suprapubic drainage. It should be noted that in children the ability to utilize office

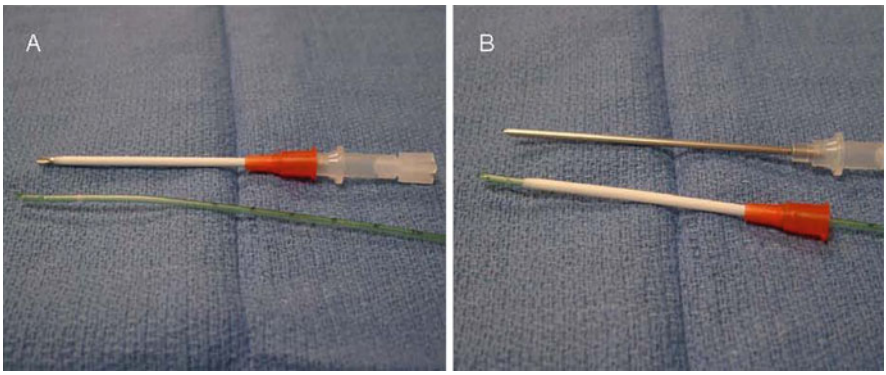

Fig. 6.3. Suprapubic catheterization. A suprapubic tube can be placed percutaneously using a 14-gauge angiocath and a 5-Fr feeding tube (**a**). Once the angiocath has been placed, the needle is removed and the 5-Fr feeding tube passes easily through the plastic cannula (**b**).

flexible cystoscopy to assist with catheter placement is quite limited (other than in the older adolescent).

Management of Indwelling Tubes and Catheters

Many children will require temporary indwelling stents or catheters. Education of the parents is essential. If the family will travel a long distance from the hospital for surgery, it is helpful to teach tube flushing or irrigation before discharge from the hospital, even for patients undergoing outpatient procedures. For example, for a simple urethral stent after hypospadias repair, we will show the parents how to insert a blunt-nosed needle into the end of the stent and flush with 3 ml saline. We then discharge them with these supplies so they will have them in case the catheter becomes plugged at a long distance from any medical help. It is also important to be certain that parents understand how to adequately tape, secure, and clean around any externalized tube such as a nephrostomy or ureteral stent.

Once patients are back in the office for removal, reassurance and talking to the patient again turns out to be the most helpful adjunct. Just as with catheterization, they are instructed about what will happen. For most externalized ureteral stents, such as those used after ureteral reimplantation, the tubes slip out simply but the patient will have modest bladder spasms or urgency for the first minute after tube removal. Warning them about this and assuring that it will go away quickly is helpful.

The most complicated tube management involves suprapubic tubes and continent cutaneous stomas after bladder augmentation when mucus is present which must be flushed and removed from the bladder. Office teaching is very important in this setting. After a healing period of 7 days, we start daily irrigation of the bladder with normal saline. A catheter tip syringe is

used to first remove all the fluid and mucus from the bladder by aspiration. Following this, 30–60 ml are first gently instilled and aspirated. Once there is significant mucus in the aspirate, this is detached from the suprapubic tube and discarded into the toilet. This flush and evacuation is repeated a minimum of six times or until the aspiration yields minimal mucus. If the patient tolerates the initial installation well, irrigation may be performed a bit more vigorously in order to detach mucus from the wall of the augmentation. In some patients, aspiration will be difficult until 50–100 ml is first instilled into the bladder to separate the walls and create a space for irrigation. Once the post-op suprapubic tube is removed, patients with bladder augmentation require chronic bladder irrigation to remove mucus and prevent formation of stones and recurring urinary tract infections. This is done with the intermittent catheter taped in place either through the stoma or urethra and then irrigation is carried out in a similar fashion. We find that having our nurse touch base with these families frequently and early on to troubleshoot and encourage good compliance is well worth the effort.

REFERENCES

1. Smith C, Smith DP. Office pediatric urologic procedures from a parental perspective. Urology 2000;55(2):272–6.
2. Anand KJ. Consensus statement for the prevention and management of pain in the newborn. Arch Pediatr Adolesc Med 2001;155(2):173–80.
3. Circumcision policy statement. American Academy of Pediatrics. Task Force on Circumcision. Pediatrics 1999;103(3):686–93.
4. Brady-Fryer B, Wiebe N, Lander JA. Pain relief for neonatal circumcision. Cochrane Database Syst Rev 2004(4):CD004217.
5. Cartwright PC, Snow BW, McNees DC. Urethral meatotomy in the office using topical EMLA cream for anesthesia. J Urol 1996;156(2 Pt 2):857–8; discussion 8–9.
6. Taddio A, Ohlsson A, Einarson TR, Stevens B, Koren G. A systematic review of lidocaine-prilocaine cream (EMLA) in the treatment of acute pain in neonates. Pediatrics 1998;101(2):E1.
7. Jayanthi VR, Burns JE, Koff SA. Postneonatal circumcision with local anesthesia: a cost-effective alternative. J Urol 1999;161(4):1301–3.
8. Hutcheson JC. Male neonatal circumcision: indications, controversies and complications. Urol Clin North Am 2004;31(3):461–7, viii.
9. Palmer LS, Palmer JS. The efficacy of topical betamethasone for treating phimosis: a comparison of two treatment regimens. Urology 2008;72(1):68–71.
10. Leung AK, Robson WL, Tay-Uyboco J. The incidence of labial fusion in children. J Paediatr Child Health 1993;29(3):235–6.
11. Myers JB, Sorensen CM, Wisner BP, Furness PD, 3rd, Passamaneck M, Koyle MA. Betamethasone cream for the treatment of pre-pubertal labial adhesions. J Pediatr Adolesc Gynecol 2006;19(6):407–11.

7 Genetic Diseases and Associated Urologic Manifestations

Jeffrey S. Palmer and Katherine C. Hubert

Abstract The diagnosis of a genetic disease is usually made through a combination of clinical characteristics and genetic testing. It is important that urologists be able to recognize the cardinal features of these disorders and identify the associated urologic manifestations. The purpose of this chapter is to provide an overview of the genetic disorders with urologic manifestations.

Keywords Genitourinary · Genetic disease · Manifestations · Genital · Urinary tract

INTRODUCTION

Genetic diseases are typically divided into two categories: those with a simple Mendelian mode of inheritance and genetically complex disorders that do not have this type of inheritance. The former group is due to abnormalities of single genes, whereas the latter arise from the interaction of multiple genes and/or genes and environmental factors. Cumulatively, these disorders have a major impact on the health of children. They may affect single or multiple organ systems, have subtle or apparent clinical manifestations in the pediatric population, and have a variety of genetic etiologies. Many genetic disorders affect the genitourinary system in which the genders share certain aspects of embryologic development.

The diagnosis of a genetic disease is usually made through a combination of clinical characteristics and genetic testing. The genitourinary manifestations of some genetic diseases may be obvious on physical examination or imaging studies, while others may require more invasive testing. It is important that urologist be able to recognize the cardinal features of these disorders and identify the associated urologic manifestations.

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The purpose of this chapter is to provide an overview of the genetic disorders with urologic manifestations. It is important, however, to refer patients to geneticists for proper counseling. Current and detailed information about the specific syndromes is available through an online database of human genes and genetic phenotypes, the Online Mendelian Inheritance in Man at http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim.

AARSKOG SYNDROME

Aarskog syndrome is an X-linked (Xp11.2) or autosomal dominant disorder that encompasses specific facial features, growth impairment, normal intelligence, short stature, short, broad webbed hands, fifth finger clinodactyly, and genital abnormalities. The facial features include round facies, hypertelorism, anteverted nares, a stubby nose with a broad nasal bridge, down-slanting palpebral fissures, a prominent philtrum, and a broad upper lip. The genital abnormalities include unilateral or bilateral cryptorchidism, infertility with normal pubertal development, and shawl scrotum a condition in which the scrotum surrounds the penis.

FAMILIAL HEMATURIA DUE TO TYPE IV COLLAGEN MUTATIONS

Alport syndrome and thin basement membrane glomerulopathy are primary genetic disorders of the glomerular basement membrane (GBM) that cause persistent hematuria of glomerular origin in children (*1*). There is diffuse thinning of the GBM in both conditions; it remains attenuated in thin basement membrane nephropathy while the GBM in Alport syndrome gets progressively thicker resulting in worsening proteinuria and renal function.

ALPORT SYNDROME

Alport syndrome is inherited in either an X-linked form (COL4A5 gene on Xq22) by males or an autosomal recessive form by either gender (COL4A3 and COL4A4 genes on 2q). A major component of the GBM, collagen type IV, is abnormal in this disease, which results in hematuria and/or chronic renal failure. Alport syndrome is seen in approximately 2.3% of renal transplant patients and 0.6–3% of patients with end-stage renal disease (*2*). This syndrome, which affects 1 in 5,000 people, is characterized by anterior lenticonus, neural hearing loss, and hereditary, progressive nephritis. The typical presentation is one of upper respiratory tract infections with subsequent persistent gross or microscopic hematuria. Renal failure occurs in the second to third decade of life (*2*). The diagnosis is confirmed by specific GBM electron microscopic features including thickening and splitting of the GBM with electron-lucent areas containing small, dense granulations.

Management consists of low-phosphate, low-protein, and low-salt diets, in addition to cyclosporine A (*2*). Renal transplant recipients may have recurrence resulting from anti-glomerular basement membrane nephritis (*3*).

THIN BASEMENT MEMBRANE NEPHROPATHY

Heterozygous mutations in type IV collagen genes COL4A3 or COL4A4 typically cause microhematuria without proteinuria or renal functional impairment, known as thin basement membrane nephropathy (*1*). Rarely this form of GBM nephropathy may lead to proteinuria and end-stage renal disease.

CONGENITAL HEPATORENAL FIBROCYSTIC SYNDROMES

The hepatorenal fibrocystic syndromes are a heterogeneous group of severe monogenic conditions that may be detected prenatally (*4*). This group includes autosomal recessive polycystic kidney disease (ARPCKD), Meckel-Gruber syndrome (MKS), Bardet-Biedl syndrome (BBS), and Jeune asphyxiating thoracic dystrophy (JATD). They commonly present in the neonatal and pediatric age groups with developmental abnormalities mostly involving the kidney and liver. Extrahepatic features include bone and central nervous system abnormalities, dysmorphic features, and developmental delay. Cystic lesions affect both liver and kidneys, with the severity of the renal lesions determining the clinical presentation and long-term prognosis of many of these syndromes.

AUTOSOMAL RECESSIVE (INFANTILE) POLYCYSTIC KIDNEY DISEASE (ARPKD)

Polycystic kidney disease includes both autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD). ARPKD is the most common neonatal polycystic kidney disease with an incidence of about 1 in 20,000. The gene has been mapped to the short arm of chromosome 6 (6p21.1-12) (*5*, *6*). Most patients (75%) present in infancy with both ectasia and cystic dilatation of the renal collecting tubules that prevent the normal development of the nephrons (*4*). The nephrons remain as primitive ducts lined by undifferentiated epithelium and sheathed with thick layers of connective tissue. The kidney appears spongy and there is no distinction between cortex and medulla. Affected fetuses have large, renoform, nonbosselated flank masses that may lead to prenatal oligohydramnios and impede vaginal delivery. Newborns may present with oliguria, Potter's facies, and respiratory distress due to pulmonary hypoplasia.

Congenital hepatic fibrosis is characteristic of ARPKD and correlates with the severity of the renal cystic disease. Younger patients with ARPKD

have milder liver disease, and, conversely, younger patients with congential hepatic fibrosis have milder cystic renal disease. Liver histology shows portal spaces enlarged by periportal fibrosis, proliferation of biliary ducts, and ductal plate malformation (*4*). The liver disease may lead to portal hypertension, esophageal varices, and hepatosplenomegaly in older children. Diagnosis may be suspected on prenatal ultrasonography by the findings of oligohydramnios and homogeneously, hyperechogenic, enlarged kidneys. The diagnosis is confirmed with computed tomography.

There is no cure for ARPKD. Approximately half of the children with this disease die within the first month of life, usually due to pulmonary complications (*7*). Management of survivors includes respiratory care and treatment of hypertension, congestive heart failure, esophageal varices, and hepatic failure. Options for renal failure include dialysis and renal transplantation.

AUTOSOMAL DOMINANT (ADULT) POLYCYSTIC KIDNEY DISEASE (ADPKD)

ADPKD is the most common renal hereditary disease, affecting 1 in 400 to 1,000 live births (*8*). It accounts for 5% of the end-stage renal disease population in the United States and Europe (*8*). Approximately 85% of affected families have mutations in the polycystic kidney disease (PKD)1 gene (*8*). ADPKD is mapped to chromosome 16 (16p13.11-16pter) and chromosome 4 with 100% penetrance (*9*). Most patients present between the ages of 30 and 50 with hypertension, flank or abdominal pain, and hematuria. Renal involvement may result in proteinuria, hypertension, calculi, and urinary tract infections. ADPKD is associated with hepatic cysts, mitral valve regurgitation, colonic diverticuli, polycythemia, and intracranial aneurysms (*10*). It is less common in the pediatric population. Neonates usually present with enlarged kidneys, congenital hepatic fibrosis, and even respiratory distress or stillbirth in those with severe disease. Children older than 1 year of age usually present with hypertension, proteinuria, and hematuria.

In contrast to ARPKD, these patients usually have large hepatic cysts, and the number of hepatic cysts can increase with the age of the patient (*4*). The biliary malformations and hepatic fibrosis that characterize ARKPKD are absent in most cases.

Diagnosis is based on DNA analysis, ultrasonography, and computed tomography of large kidneys with thin-walled cysts. Amniocentesis and chorionic villae sampling may be used for prenatal diagnosis of ADPKD. The treatment consists of conservative management and supportive care.

BARDET-BIEDL SYNDROME

Bardet-Biedl syndrome is a genetic disorder with the primary features of obesity, polydactyly, pigmentary retinopathy, hypogonadism, renal

anomalies, and developmental delay (*11*). Secondary features include diabetes, hypertension, and congenital heart defects (*11*). Renal dysplasia progressing to end-stage renal disease is the most significant urologic manifestation and the main cause of morbidity and mortality (*12*). Other genitourinary manifestations include septate vagina, hypogonadism, hemocolpos, uterine duplication, urogenital sinus abnormalities, and hypoplastic fallopian tubes, ovaries, and uterus (*13*). It was originally thought to be a single locus autosomal recessive disorder but has since been proven to be a genetically heterogeneous disease caused by multiple individual loci (*11*). Bardet-Biedl syndrome is diagnosed by clinical evaluation, linkage analysis and polymerase chain reaction (PCR) (*14*).

JEUNE SYNDROME (ASPHYXIATING THORACIC DYSPLASIA)

Renal, hepatic, and pancreatic abnormalities are common in Jeune syndrome (*4*). It is a rare autosomal recessive condition characterized by skeletal abnormalities, including a long and narrow thorax, metaphyseal irregularities, shortness of the ribs and long bones, and, occasionally, polydactyly (*4*, *15*). The urologic manifestations include renal cysts and chronic tubulointerstitial renal lesions (*16*). Chronic renal failure occurs in the 20% of patients who survive beyond the neonatal period. Renal transplantation is an option for patients with renal failure. Hepatic involvement can manifest as neonatal cholestasis or hepatic fibrosis leading to biliary cirrhosis and portal hypertension (*4*).

MECKEL-GRUBER SYNDROME

Meckel-Gruber syndrome is a uniformly lethal malformation syndrome characterized by a triad of central nervous system abnormalities (prosencephalic dysgenesis, occipital encephalocele, and rhombic roof dysgenesis), large multicystic kidneys, bilateral polydactyly, and fibrocystic changes of the liver (*4*). Other features include ambiguous genitalia and cardiac abnormalities. Early prenatal diagnosis is essential in parental counseling since newborns die immediately after birth. Prenatal ultrasonography of this syndrome can be made as early as 11 weeks of gestation (*17*).

BRANCHIO-OTO-RENAL SYNDROME (MELNICK-FRASER SYNDROME)

Branchio-oto-renal syndrome is an autosomal dominant disorder with an estimated prevalence of 1 in 40,000 (*18*). It is a heterogeneous condition characterized by ear malformations, hearing impairment, branchial fistulae and cysts, preauricular pits, and renal malformations (*19*, *20*). Although

the diagnosis can be made based on clinical criteria alone, about 40% of patients show variations in the EYA1 gene on chromosome 8 (8q13.3). The renal anomalies include renal agenesis, renal hypoplasia and dysplasia, hydronephrosis, caliectasis, pelviectasis, vesicoureteral reflux, ureteropelvic junction obstruction, and calyceal diverticulae and cysts. Approximately 6% of patients progress to renal failure. There is a high rate of fetal deaths possibly due to bilateral renal agenesis (*21*).

CHARGE SYNDROME

CHARGE is a multisystemic syndrome that consists of *c*olobomata, *h*eart defects, choanal *a*tresia, *r*etarded growth and development, *g*enital hypoplasia, and *e*ar anomalies (*22*). The exact pattern of inheritance is unclear. The genitourinary manifestations include neurogenic bladder, hydronephrosis, vesicoureteral reflux, and ureteropelvic junction obstruction (*23*). All patients should have bladder and renal ultrasonography and a voiding cystourethrogram. The female genital manifestations include absent vagina, ovaries, and uterus, and hypoplasia of the labia majora, labia minora, and/or clitoris. The male genital manifestations include micropenis, penile agenesis, cryptorchidism, bifid scrotum, penile chordee, and hypospadias.

EHLERS-DANLOS SYNDROME

Ehlers-Danlos syndrome is an autosomal recessive connective tissue disorder characterized by poor wound healing, skin hyperextensibility, joint hypermobility, and hernias. The urologic manifestations include hydroureter and bladder diverticulae. A conservative approach to the bladder diverticulae is recommended due to the risk for poor wound healing and bleeding (*24*). Ehlers-Danlos bladder diverticulae form a distinct group characterized by postoperative recurrence (*25*). They may cause difficulties with micturition and infection. Surgery should be considered in children with upper tract deterioration and uncontrolled urinary tract infections.

FRASER SYNDROME (CRYPTOPHTHALMOS SYNDROME)

Fraser syndrome is an autosomal recessive syndrome characterized by genitourinary and craniofacial abnormalities, syndactyly, and cryptopthalmos. Unilateral or bilateral renal agenesis, which occurs in 85% of patients, is a major cause of early death (*26*). Males most commonly have hypospadias, micropenis, and cryptorchidism (*27*). Females typically have bicornate uterus, clitoral hypertrophy, and vaginal atresia, and prenatal ultrasonography may diagnose this condition as early as 18 weeks of gestation.

GOLDENHAR SYNDROME (OCULO-AURICULAR VERTEBRAL COMPLEX)

The Goldenhar syndrome is a complex of unilateral craniofacial and vertebral abnormalities with an unclear pattern of inheritance. Signs associated with this syndrome include preauricular skin tags, cleft palate, maxillary or mandibular hypoplasia, ear microtia, facial asymmetry, and epibulbar dermoids (*28*). This syndrome also includes anomalies of the cardiac, neural, pulmonary, and genitourinary systems (*28*). Ritchey et al. reported a 70% (14 of 20 cases) incidence of urinary tract abnormalities including five cases of vesicoureteral reflux (*29*). Other genitourinary manifestations include renal ectopia, renal agenesis, ureteropelvic junction obstruction, multicystic dysplastic kidney, ureteral duplication, and left retrocaval ureter (*29*).

HYPERTELORISM-HYPOSPADIUS SYNDROME (OPITZ G/BBB SYNDROME)

Hypertelorism-Hypospadius syndrome is characterized by midline anomalies, including hypertelorism, cleft lip/palate, and hypospadias. Urologic abnormalities include splayed labia majora, vesicoureteral reflux, unilateral and bilateral cryptorchidism, bifid scrotum, micropenis, hypoplastic scrotum, and other ureteral and renal anomalies (*30*). Other characteristics include patent ductus arteriosis, swallowing defects, and developmental delay (*31*). It is inherited in an autosomal dominant pattern linked to chromosome 22 (2q11.2) and in an X-linked pattern (Xp22).

INTERSEX DISORDERS

The intersex disorders encompass pseudohermaphroditism, true hermaphroditism, and gonadal dysgenesis. Chromosomal analysis is indicated in any child with ambiguous genitalia. Genetic females with ambiguous genitalia should also obtain urinary renin, 17-α-hydroxysteroids, and 17-α-ketosteroids, and serum 17-α-hydroxyprogesterone.

LESCH-NYHAN SYNDROME

Lesch-Nyhan syndrome is an X-linked recessive disorder that results from a partial or complete deficiency of the enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT) (*32*). HGPRT catalyzes the conversion of hypoxanthine to inosinic acid and guanine to guanylic acid in the presence of phosphoribosylpyrophosphate (*33*). The syndrome is characterized by excessive uric acid production, marked hyperuricemia, and hyperuricosuria due to a change in this pathway. Other features include choreoathetosis, mental and growth retardation, spasticity, and self-mutilation. These children typically appear normal at birth until they develop the aforementioned

features late in the first year of life. Both hyperuricemia with associated gouty arthritis and hyperuricemic nephropathy can be prevented by the use of allopurinol, a xanthine oxidase inhibitor (*33*). The urologic manifestations include renal calculi composed of uric acid. Treatment is aimed at preventing additional uric acid stone formation by decreasing the degree of urate and uric acid supersaturation in the urine and by blocking steps in uric acid production. It is also important to modify the diet, fluid intake, and urine pH (*34*).

MENKES DISEASE

Menkes disease is a lethal, sex-linked recessive (Xq12-13) neurodegenerative disorder that is associated with abnormalities in copper transport and urine and serum levels. Characteristics of the disease include kinky, colorless, and friable hair, hypotonia, myoclonic seizures, mental retardation, failure to thrive, hypothermia, spasticity, osteoporosis, arterial tortuosity, and chubby, rosy cheeks (*35*). The genitourinary abnormalities include cryptorchidism, bladder diverticulae, hydronephrosis, and vesicoureteral reflux (*36*). A conservative treatment approach is used due to the poor prognosis of this disease.

MURCS SYNDROME

MURCS is a syndrome of a group of associated congenital anomalies without a clear pattern of inheritance: *mu*llerian duct aplasia, *r*enal aplasia, and *c*ervicothoracic *s*omite dysplasia (*37*). The most common presentation is primary amenorrhea. Normal secondary sexual characteristics and an absent vagina are noted on physical examination. The most common radiologic findings are renal agenesis with an ectopic contralateral kidney that is usually pelvic in location, and fusion of cervical and upper thoracic vertebrae.

NAIL-PATELLA SYNDROME (HEREDITARY OSTEOONYCHODYSPLASIA)

Nail-patella syndrome is a rare autosomal dominant syndrome linked to chromosome 9 (9q34). It is characterized by the presence of dysplastic nails, hypoplastic or absent patellae, radial head dislocations, iliac horns, and heterochromia of the iris (Lester's sign) (*2*, *38*). Renal disease, seen in 30–50% of patients, includes proteinuria, microhematuria, renal failure, and nephrotic syndrome (*2*, *39*). Ultrastructural changes on renal biopsy include an irregularly thick GBM, with patches of dense fibrillar material. The severity of the child's renal disease does not depend upon the degree of parental renal involvement (*40*). Renal transplantation may be considered in

patients with renal failure. The diagnosis is made in children using skeletal ultrasonography and renal biopsy. Prenatal diagnosis is confirmed by ultrasonographic findings of iliac horns as this is a pathognomic finding.

NOONAN SYNDROME

Noonan syndrome is an autosomal dominant disorder in males that is similar to Turner syndrome in females. It is characterized by webbed neck, mild mental retardation, hypertelorism, low posterior hairlines, low-set ears, short stature, deeply grooved philtrum, chest deformities, lymphedema, congenital heart defects, and bleeding abnormalities (*41*). This syndrome is associated with cryptorchidism. Adults may occasionally be fertile.

OCULOCEREBRORENAL SYNDROME OF LOWE

Oculocerebrorenal Syndrome of Lowe is an X-linked recessive syndrome (OCRL1 gene at Xq24-26) involving the eyes, central nervous system, and kidneys (*42*). The clinical features include growth retardation, severe mental retardation, areflexia, hypotonia, noninflammatory joint swelling of unknown cause, and renal tubular dysfunction (Fanconi's syndrome) (*43*). The manifestations of Fanconi's syndrome are proteinuria, metabolic acidosis, aminoaciduria, and hyperphosphaturia. The ocular findings include cataracts, glaucoma, and corneal keloids (*43*). Female carriers have lenticular opacities on slit-lamp examination of the cortex of the lens. Patients often exhibit an unusual facial appearance with frontal bossing, progressive facial elongation, deep-set eyes, and chubby cheeks (*43*).

PRADER-WILLI SYNDROME

Prader-Willi syndrome is the most common form of obesity caused by a genetic syndrome with an incidence of approximately 1 in 25,000 births (*44*). The chromosomal abnormality is a deletion in the paternal chromosome in the region of 15q11-13 (*45*, *46*). Infants typically have difficulty feeding with resultant failure to thrive in the first year of life. Newborns may have nonspecific findings including hypotonia, poor sucking reflex, diminished or absent cry, and somnolence. There is a delay in early developmental milestones, and after 1 year of age, there is a transition to hyperphagia. The male genital manifestations include cryptorchidism, micropenis, hypogonadism, and scrotal hypoplasia. Hypogonadism is thought to be due to hypothalamic dysfunction. Typical characteristics in females include hypoplastic labia minora and clitoris, infertility, delayed menarche, and abnormal pubertal development. Other manifestations of this syndrome are a downturned mouth, a narrow nasal bridge, small hands and feet, and a narrow bifrontal diameter. Prenatal diagnosis is confirmed by amniocentesis and chorionic villae sampling. If the diagnosis is suspected in infants

or children, a high-resolution karyotype followed by methylation studies specific for Prader-Willi Syndrome should be obtained (*44*). Treatment consists of hormonal therapy and weight control.

PRUNE BELLY SYNDROME (EAGLE-BARRETT SYNDROME)

Prune belly syndrome presents with three main features: abdominal wall flaccidity, bilateral intra-abdominal cryptorchidism, and urologic abnormalities (*47*). The abdominal wall flaccidity may cause lordosis and respiratory infections. The cryptorchid testes, if left untreated, do not demonstrate spermatogenesis after puberty. The vesical and ureteral smooth muscle develops abnormally resulting in a large hypotonic bladder, tortuous and dilated ureters, and vesicoureteral reflux in two-thirds of patients. Other urologic manifestations include hydronephrosis, renal dysplasia, patent urachus, congenital megalourethra, and prostatic hypoplasia. There are also cardiac, gastrointestinal, pulmonary, and orthopedic abnormalities (*48*). The syndrome has been reported in female patients (*49*).

The management of this condition includes diagnostic evaluation of cardiopulmonary function, and treatment of the vesicourethral dysfunction, cryptorchidism, and vesicoureteral dysfunction, and abdominal wall reconstruction. Early simultaneous correction of Prune Belly syndrome abnormalities with individualized urinary reconstruction, abdominoplasty, and orchiopexy is feasible and provides excellent long-term results (*47*). The exact pattern of inheritance is unclear.

ROBINOW SYNDROME (FETAL FACE SYNDROME)

Robinow syndrome is a type of dwarfism with mesomelic limb shortening, hemivertebrae, and genital hypoplasia (*50*). Both autosomal dominant and autosomal recessive inheritance have been described suggesting that there is allelic heterogeneity (*51*). It is associated with prominent nares, hypertelorism, a short upturned nose, low set ears, depressed nasal bridge, rib abnormalities, and spinal abnormalities (*52*). In females, there is reduced clitoral size, hypoplasia of the labia minora, vaginal atresia, and hematocolpos (*50*). The urologic manifestations in males include cryptorchidism and a hypoplastic or absent penis (*51*, *52*).

SICKLE CELL DISEASE

Sickle cell disease is due to the inheritance of abnormal hemoglobin S rather than adult hemoglobin A. The single point mutation at the sixth residue of the β-chain causes intracellular polymerization of hemoglobin, resulting in the manifestations of sickle cell disease: painful crises, cerebrovascular accidents, bony and pulmonary infections, and swelling of the spleen and extremities (*2*). The renal manifestations include hematuria,

tubular dysfunction, and proteinuria. The high osmolality, low pO_2, and low pH in the medulla promote the "sickling phenonmenon," which produces vascular obstruction, proximal congestion, and erythrocyte extravasation, resulting in hematuria (*2*). Tubular dysfunction is due to alterations in the medually area. Glomerular and capillary hypertension cause glomerular hypertrophy, focal segmental glomerulosclerosis, proteinuria, and progressive decline of renal function with age. The most significant genital manifestation is low-flow priapism, which can cause fibrosis of the corporal cavernosa. Conservative treatment includes pain control, aggressive hydration, oxygenation, and metabolic alkalinization. Aspiration and irrigation with epinephrine, hypertransfusion, and erythrophoresis may be required.

SMITH-LEMLI-OPITZ SYNDROME

Smith-Lemli-Opitz syndrome is an autosomal recessive syndrome caused by a 7-dehydrocholesterol reductase deficiency (*53*, *54*). It is characterized by 2/3 toe soft tissue syndactyly, micrognathia, mental retardation, holoprosencephaly, low levels of cholesterol, self-mutilation, low-set ears, microcephaly, and elevated levels of 7-dehydrocholesterol. Approximately 91% of males have genital abnormalities such as hypospadias, cryptorchidism, ambiguous genitalia, and sex reversal (*55*). The genitourinary manifestations include renal agenesis, hypoplastic kidneys, cystic kidneys, and hydronephrosis. Prenatal diagnosis is confirmed by amniocentesis or chorionic villus sampling.

TURNER SYNDROME

Turner syndrome is the most common sex chromosome abnormality in females, manifesting as either a 45, X karyotype or a mosaic 45, X/46, XX karyotype. Structural aberrations of the X-chromosome may also cause this syndrome. Clinical features include short stature, shield chest, webbed neck, bicuspid aortic valve, cubitus valgus of the elbow, congenital lymphedema, and coarctation of the aorta (*56*). The genital manifestations include primary amenorrhea and streak ovaries. The most common associated renal abnormality is horseshoe kidney. Other renal anomalies include hydronephrosis, duplications, malrotation, and nonfunctioning kidney. Renal ultrasonography should be obtained in all patients.

VACTERL ASSOCIATION

VACTERL association is a group of associated congenital anomalies that is often lethal: *v*ertebral effects, *a*nal atresia, *c*ardiac defects, *t*racheo*e*sophagel fistula, *renal malformations*, and *l*imb defects (*57*, *58*). At least three of these abnormalities are required for diagnosis (*59*). Urologic manifestations include hypospadias and renal anomalies, including renal

agenesis, vesicoureteral reflux, obstructive lesions, and cystic renal disease (*60*). The exact pattern of inheritance of this condition has not been delineated.

WILMS TUMOR (NEPHROBLASTOMA)

Wilms tumor is a solid childhood malignancy with a peak incidence between ages 3 and 4 (*61*). There are three associated genetic syndromes: Denys-Drash syndrome, WAGR syndrome, and Beckwith-Wiedemann syndrome. The former includes male Wilms tumor, pseudohermaphroditism, and diffuse mesangial sclerosis of the kidney (*62*). WAGR syndrome consists of *W*ilms tumor, *a*niridia, *g*enitourinary anomalies (including male pseudohermaphroditism), and mental *r*etardation. The characteristics of Beckwith-Wiedemann syndrome include Wilms tumor, hemihypertrophy, mental retardation, macroglassia, microcephaly, visceromegaly, and omphalocele. The WT1 gene on chromosome 11 has been identified as the etiology for both WAGR syndrome and Denys-Drash syndrome The WT2 gene on chromosome 11 is responsible for Beckwith-Wiedemann syndrome. Treatment involves surgery, radiation therapy, and chemotherapy.

ZELLWEGER SYNDROME (CEREBROHEPATORENAL SYNDROME)

The characteristics of Zellweger syndrome include hypotonia, epileptic seizures, a high forehead, a large anterior fontanelle, shallow orbital ridges, micrognathia, and hepatomegaly. It is inherited in an autosomal recessive fashion. The most common urologic manifestation is renal cystic disease (*63*). Prenatal diagnosis involves chorionic villus sampling detecting very long-chain fatty acids.

RECENTLY DEFINED GENETIC SYNDROMES

Pelvis Syndrome

PELVIS syndrome has the characteristic findings of perineal hemangioma, external genital manifestations, lipomyelomeningocele, urinary tract abnormalities, imperforate anus, and skin tag (*64*). Urinary tract abnormalities include renal agenesis, vesicoureteral reflux, and bladder anomalies. Malformations of the external genitalia include penile chordee, bifid scrotum, and vulvar hypertrophy or hypotrophy.

IMAGe

IMAGe is a syndrome that consists of *i*ntrauterine growth retardation, *m*etaphyseal dysplasia, *a*drenal hypoplasia congenita, and *g*enital anomalies (*65*). The genital abnormalities include bilateral cryptorchidism and a small phallus.

REFERENCES

1. Kashtan CE, *Familial hematuria due to type IV collagen mutations: Alport syndrome and thin basement membrane nephropathy*. Curr Opin Pediatr 2004. **16**: 177–181.
2. Saborio P, Scheinman J, *Genetic renal disease*. Curr Opin Pediatr 1998. **10**: 174–183.
3. Kashtan CE, Gubler M, Sisson-Ross S, et al. *Chronology of renal scarring in males with Alport syndrome*. Pediatr Nephrol 1998. **12**: p. 269–274.
4. Johnson CA, Gissen P, Sergi C, *Molecular pathology and genetics of congenital hepatorenal fibrocystic syndromes*. J Med Genet 2003. **40**: 311–319.
5. Cole BR, Conley S, Stapleton FB, *Polycystic kidney disease in the first year of life*. J Pediatr 1987. **111**: 693.
6. Zerres K, Mücher G, Bachner L, *Mapping of the gene for autosomal recessive polycystic kidney disease (ARPKD) to chromosome 6p21-cen*. Nature Genet 1994. **7**: 429–432.
7. Zerres K, Rudnik-Schoneborn S, Deget F, et al, *Clinical course of 115 children with autosomal recessive polycystic kidney disease*. Acta Paediatr 1996. **85**: 437–445.
8. Rizk D, Chapman A, *Core curriculum in nephrology: cystic and inherited kidney diseases*. Am J Kidney Dis 2003. **42**(6): 1305–1317.
9. Peters DJM, Saris JJ, et al, S.L.*Chromosome 4 localization of a second gene for autosomal dominant polycystic kidney disease*. Nature Genet 1993. **5**: p. 359.
10. Beebe DK, *Autosomal dominant polycystic kidney disease*. Am Fam Physician 1996. **15**: 925–931.
11. Sheffield VC, *Use of isolated populations in the study of a human obesity syndrome, the Bardet-Biedl syndrome*. Pediatr Res 2004. **55**(6): 908–911.
12. Pevarajan D, *Letter to the editors: Obesity and genitourinary anomalies in Bardet-Biedl syndrome after renal transplantation*. Pediatr Nephrol 1995. **9**: 397–402.
13. Stoler JM, Herrin J, Holmes LB, *Genital abnormalities in females with Bardet-Biedl syndrome*. Am J Med Genet 1995. **55**: 276–278.
14. Beales PL, Warner G, Thakker R, et al, *Bardet-Biedl syndrome: a molecular and phenotypic study of 18 families*. J Med Genet 1997. **34**: 92–98.
15. Chen CP, Lin S, Jan SW, et al, *Prenatal diagnosis of asphyxiating thoracic dysplasia (Jeune syndrome)*. Am J Perinatol 1996. **13**: 495–498.
16. Amirou M, Bourdat M, Huet G, et al, *Successful renal transplantation in Jeune syndrome type 2*. Pediatr Nephrol 1998. **12**: 293–294.
17. Sepulveda W, Sebire N, Souka A, et al, *Diagnosis of the Meckel-Gruber syndrome at eleven to fourteen weeks gestation*. Am J Obstet Gynecol 1997. **176**: 316–319.
18. Zar T, Aglieco F, Ranga KV, *Quiz page April 2008: deafness, preauricular pits and renal failure. BOR syndrome or Melnick-Fraser syndrome*. Am J Kidney Dis 2008. **51**(4): p. A44–6.
19. Melnick M, Bixler D, Silk K, et al, *Autosomal dominant brachiotorenal dysplasia.* For the National Foundation – March of DIMES. BD: OAS XI 1975. **5**: 1212–1228.
20. Chen A, Francis M, Ni L, et al, *Phenotypic manifestations of branchiootorenal syndrome*. Am J Med Genet 1975. **58**: 365–370.
21. Misra M, Nolph KD, *Renal failure and deafness: branchio-oto-renal syndrome*. Am J Kidney Dis 1998. **32**: 334–337.
22. Pagon RA, Graham J, Zonana J, et al, *Coloboma, congenital heart disease and choanal atresia with multiple anomalies: CHARGE association*. J Pediatr 1981. **99**: 223–237.
23. Ragan DC, Casale A, Rink R, et al, *Genitourinary anomalies in the CHARGE Association*. J Urol 1999. **161**: 622–625.
24. Stage HH, Tank E, *Primary congenital bladder diverticula in boys*. Urology 1992. **40**: 536.
25. Levard G, Aigrain Y, Ferkadji L, Elghoneimi A, Pichon J, Boureau M, *Urinary bladder diverticula and the Ehlers-Danlos syndrome in children*. J Pediatr Surg 1989. **24**(11): 1184–86.
26. Lurie IW, Cherstvoy E, *Renal agenesis as a diagnostic feature of the cryptopthalmos-syndactyly syndrome*. Clin Genet 1984. **25**: 528–532.
27. Sarmon G, Speer M, Rudolph AJ, *Fraser syndrome (cryptopthalmos [hidden eye]-syndactyly syndrome)*. J Perinatol 1995. **15**: 503–506.

28. Ishitoya S, Arai Y, Waki K, Okubo K, Suzuki Y, *Left Retrocaval Ureter Associated with the Goldenhar Syndrome (Branchial Arch Syndrome)*. J Urol 1997. **158**(2): 572–573.
29. Ritchey ML, Norbeck J, Huang C, et al, *Urologic manifestations of Goldenhar syndrome*. Urology 1994. **43**: 88–91.
30. Jacobson Z, Glickstein J, Hensle T, et al, *Further delineation of the Opitz G/BBB syndrome: report of an infant with complex congenital heart disease and bladder exstrophy, and review of the literature*. Am J Med Genet 1998. **78**: 294–299.
31. Robin NH, Opitz J, Muenke M, *Opitz G/BB syndrome: clinical comparisons of families linked to Xp22 and 22q, and a review of the literature*. Am J Med Genet 1996. **62**: 305–317.
32. Painter MJ, Bergman I, *Neurology*, in *Nelson Essentials of Pediatrics*. 1990, WB Saunders: Philadelphia. p. 654.
33. Crawhall JC, Henderson J, Kelley WN, *Diagnosis and treatment of the Lesch-Nyhan syndrome*. Pediatr Res 1972. **6**: 504–513.
34. Williams-Larson AW, *Urinary calculi associated with purine metabolism. Uric acid nephrolithiasis*. Endocrinology and Metabolism Clinics of North America 1990. **19**(4): 821–38.
35. Nicholos BL, *Pediatric nutrition and nutritional disorders*, in *Nelson Essentials of Pediatrics*. 1990, WB Saunders: Philadelphia. p. 84.
36. Daly WJ, Rabinovitch H, *Urologic abnormalities with Menkes syndrome*. J Urol 1981. **126**.
37. Duncan PA, Shapiro L, Stangel JJ, et al, *The MURCS association: mullerian duct aplasia, renal aplasia, and cervicothoracic somite dysplasia*. J Pediatr 1979. **95**: 399–402.
38. Bodziak KA, Hammond W, Molitoris BA, *Inherited diseases of the glomerular basement membrane*. Am J Kidney Dis 1994. **23**: 605–618.
39. Schmeider G, Freitag DS, *The nail-patella syndrome*. Am Fam Physician 1988. **38**: 193–194.
40. Looji BJ, TeSlaa R, Hogewind BL, et al, *Genetic counseling in the hereditary osteo-onychodysplasia (HOOD, nail-patella syndrome) with nephropathy*. J Med Genet 1988. **25**: 682–686.
41. Nora JJ, Nora A, Sinha AK, et al, *The Ullrich-Noonan syndrome (Turner phenotype)*. Am J Dis Child 1974. **127**: 48–55.
42. Lin T, Lewis R, Nussbaum RL, *Molecular confirmation of carriers for Lowe syndrome*. Opthalmology 1999. **106**: 119–122.
43. Lavin CW, McKeown CA, *The oculocerebral syndrome of Lowe*. Int Ophthalmol Clin 1993. **33**(2): 179–91.
44. Wattendorf DJ, Muenke M, *Prader-Willi Syndrome*. Am Fam Physician 2005. **72**: 827–30.
45. Brondum-Nielson K, *The genetic basis for Prade-Willi syndrome: the importance of imprinted genes*. Acta Pediatr 1997. **423 (suppl)**: 55–57.
46. Jiang YH, Tsai T, Bressler, et al, *Imprinting in Angelman and Prader-Willi syndromes*. Curr Opin Genet Dev 1998. **8**: 334–342.
47. Denes FT, Arap M, Giron AM, Silva FAQ, Arap S, *Comprehensive Surgical Treatment of Prune Belly Syndrome: 17 Years' Experience with 32 Patients*. Urology 2004. **64**: 789–794.
48. Geary DF, MacLusky I, Churchill BM, et al, *A broader spectrum of abnormalities in the prune belly syndrome*. J Urol 1986(135): 324.
49. Rabinowitz R, Schillinger J, *Prune belly syndrome in the female subject*. J Urol 1977. **118**: 454.
50. Patton MA, Afzal A, *Robinow syndrome*. J Med Genet 2002. **39**: 305–310.
51. Teebi AS, *Autosomal recessive Robinow syndrome*. Am J Med Genet 1990. **35**: 64–68.
52. Butler MG, Wadlington WB, *Robinow syndrome: report of two patients and review of the literature*. Clin Genet 1987. **31**: 77–85.
53. Wassif CA, Maslen C, Kachelili-Linjewile S, et al, *Mutations in human sterol delta 7-reductase gene at 11q12-13 cause Smith-Lemli-Opitz syndrome*. Am J Hum Genet 1998. **63**: 55–62.

54. Fitzky BU, Witsch-Baumgartner M, Erdel M, et al. *Mutations in the Delta7-sterol reductase gene in patients with the Smith-Lemli-Opitz syndrome*. *Proc Natl Acad Sci USA* 1998. **95**(14): 8181–8186.
55. Ryan AK, Bartlett K, Clayton P, et al, *Opitz syndrome: a variable clinical and biochemical pheonotype*. J Med Genet 1998. **35**: 558–565.
56. Saenger P, *Turner's syndrome*. N Engl J Med 1996. **335**: 1749–1754.
57. Quan L, Smith D, *The VATER association*. J Pediatr 1973. **82**: 104–107.
58. Shaw-Smith C, *Oesophageal atresia, tracheo-oesophageal fistula, and the VACTERL association: review of genetics and epidemiology*. J Med Genet 2005. **43**: 545–554.
59. Czeizel A, Ludányi I, *An aetiological study of the VACTERL-association*. Pediatrics 1985. **144**: 331–337.
60. Khoury MJ, Cordero J, Greenberg F, et al, *A population study of the VACTERL association: evidence for its etiologic heterogeneity*. Pediatrics 1983. **71**: 815–820.
61. Pritchard-Jones K, Fleming S, Davidson D, et al, *The candidate Wilms' tumour gene is involved in genitourinary development*. Nature 1990. **346**: 194–197.
62. Pelletier J, Bruening W, Kashtan CE, et al, *Germline mutations in the Wilms' tumor suppressor gene are associated with abnormal urogenital development in the Denys-Drash syndrome*. Cell 1991. **67**: 437–447.
63. Al-Essa M, Dhaunsi G, Rashed M, et al, *Zellweger syndrome in Saudi Arabia and its distinct features*. Clin Pediatr 1999. **38**: 77–86.
64. Girard C, Bigorre M, Guillot B, Bessis D, *PELVIS Syndrome*. Arch Dermatol 2006. **142**: p. 884–888.
65. Vilain E, Le MM, Lecointre C, Desangles F, Kay MA, Maroteaux P, McCabe ER, *IMAGe, a New Clinical Association of Intrauterine Growth Retardation, Metaphyseal Dysplasia, Adrenal Hypoplasia Congenita, and Genital Abnormalities.* J Clin Endocrinol Metab 1999. **84**(12): 4335–4340.

II Genitalia

8 Penis and Scrotum: Congenital and Acquired Anomalies

Jeffrey S. Palmer

Abstract Anomalies of the penis and scrotum are common and may be congenital, acquired, or iatrogenic. The understanding of the normal anatomy of the penis and scrotum is important in order to assist in evaluating congenital and acquired anomalies of the male genitalia. The purpose of this chapter is to describe the normal anatomy and anomalies of the penis and scrotum.

Keywords Penis · Scrotum · Anomaly · Anatomy · Pediatrics

INTRODUCTION

Anomalies of the penis and scrotum are common and may be congenital, acquired, or iatrogenic. The understanding of the normal anatomy of the penis and scrotum is important in order to assist in evaluating congenital and acquired anomalies of the male genitalia. The normal anatomy of the penis includes the prepuce (foreskin), glans, urethral meatus, coronal sulcus, and penile shaft. The median raphe of the penile shaft is contiguous with the scrotal raphe.

The purpose of this chapter is to describe the normal anatomy and anomalies of the penis and scrotum. Congenital anomalies may result from a disorder of sexual and/or genital differentiation, or genital growth and may be associated with other organ systems or other syndromes. Acquired conditions may result from infections and obesity, while iatrogenic conditions may be due to circumcision and other penile surgeries.

PENILE ANOMALIES

Penile length increases with gestational age (*1*, *2*) and during the first 3 months of life. After 3 months of age, penile length increases more slowly until adolescence when the length significantly increases again until the final

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size of the phallus is reached. The normal penile size is 3.5 ± 0.7 cm in the stretched length and 1.1 ± 0.2 cm in diameter in full-term male newborn compared to 13.3 ± 1.6 cm at adulthood. Tanner stages are a set of recognizable changes that occur to penis, pubic hair, and testicles during puberty. These stages along with penile length are useful in evaluating patients.

PREPUCE (FORESKIN)

Phimosis and Paraphimosis

Phimosis is the inability to partially or completely retract the foreskin. At birth, a physiologic phimosis exists due to natural adhesions between the inner preputial skin and glans and/or due to a preputial ring. The separation of the prepuce from the glans results from accumulation of epithelial debris (e.g., smegma) during the first 3–4 years of age under the foreskin, and intermittent penile erections. Primary phimosis is almost always resolvable without intervention during childhood. This results from preputial retractability increasing with age with 90% and greater than 99% of uncircumcised boys 3 and 17 years of age, respectively, with completely retractable prepuces (*3*, *4*). Secondary phimosis can result from forceful retraction and balanitis xerotica obliterans (BXO). The former is usually not recommended for it can result in a preputial cicatrix.

There are several penile issues associated with the uncircumcised penis, including paraphimosis, urinary tract infection, infection, and cancer. Paraphimosis, the entrapment of the foreskin behind the glans penis, should be treated as soon as possible for it can result in gangrene. The treatment options include manipulation, dorsal slit procedure, and circumcision.

The need to increase preputial retractability include persistent primary or secondary phimosis, primary phimosis, posthitis (i.e., inflammation of the prepuce), balanitis, and urinary tract infections. Topical corticosteroid creams have been successfully used to treat phimosis. Palmer and Palmer compared the efficacy of topical betamethasone treatment with respect to outcome and complications (*5*). Children treated twice daily for 30 days (i.e., 60 doses) or three times daily for 21 days (63 doses) had similar results – 84.5 and 87% response rate, respectively. Only one child had an untoward effect (candidal dermatitis).

Circumcision

There is a diverse view of circumcision based on nationality, culture, ethnicity, and religion (*6*). Several techniques for newborn circumcision are available, including Plastibell device, Gomco clamp, and Mogen clamp. These devices as well as others may provide a cosmetically acceptable circumcised penis. One must first completely separate the foreskin from glans in order to completely visualize the meatus to confirm that there are no anomalies, including hypospadias. Local anesthesia is recommended

when neonatal circumcision is performed (e.g., topical application of a cream containing eutectic mixture of local anesthetic (EMLA; lidocaine and prilocaine)), dorsal penile nerve block, and a penile ring block (*7*). Although circumcision can be performed under local anesthesia even in older boys, typically older infants and children have the procedure performed under general anesthesia using a free-hand sleeve resection technique.

Circumcision should not be performed in the office when the child has other penile conditions that require surgical correction, including hypospadias, dorsal hood deformity, penile curvature, webbed penis, and buried penis (refer to corresponding sections). Circumcision has several potential benefits including the prevention of phimosis, urinary tract infection (UTI), penile cancer, and sexually transmitted diseases.

Circumcision Complications

The risk of complications after circumcision, which can occur immediately or months to years later, is 0.2–5% (*8*, *9*). Bleeding is the most common complication, which occurs in 0.1% and is more commonly seen in older children. The cause of bleeding is usually from the frenulum or less frequently from a large blood vessel on the penile shaft. Although bleeding is usually self-limiting, compression, cautery, or a suture may be required. Wound infection, a rare complication, is usually prevented with the application of antibiotic ointment (e.g., bacitracin) after the procedure. If the edges of the penile skin do not adhere to the mucosal collar or if excess amount of skin is removed, penile degloving can occur. The application of antibiotic ointment to the denuded region and warm bathes will usually result in epithelization of the defect along the penile shaft. Immediate suturing of the skin edges is not recommended.

Meatal Stenosis

Meatal stenosis can be congenital, which occurs primarily in neonates with hypospadias, or acquired. Acquired meatal stenosis is a condition that occurs almost only in circumcised children. The normal urethral meatus is 14 French after 10 years of age; 12 French from 4 to 10 years of age; and 10 French prior to 4 years of age (*10*). Balanitis xerotica obliterans (BXO) is another cause of meatal stenosis (refer to BXO section). Symptoms of meatal stenosis include typical urinary stream deviation in an upward direction, penile pain at the initiation of urination, and a high velocity, narrow urinary stream. Urinary tract imaging may be indicated for associated urinary incontinence or UTI. Meatotomy or meatoplasty to treat secondary meatal stenosis can be performed by making a ventral incision long enough to create a normal meatal caliber. The suturing of the urethral mucosa to the glans reduces the risk of recurrence.

Glanular Adhesions and Skin Bridges

Glanular adhesions and skin bridges are attachments of the glans and penile shaft, which are common complications associated with circumcision. Glanular adhesions are attachments between the circumcision incision line or inner prepuce attaching to the glans. Persistent adhesions can be lysed in the office with the application of topical analgesia such as EMLA cream. Low-dose steroids have been relatively unsuccessful in lysing adhesions. Skin bridges (Fig. 8.1) are epithelized adhesions. Skin bridges can lead to penile torsion and chordee and torsion, which may require excision in the operating room under general anesthesia.

Fig. 8.1. Penile skin bridge between the penile shaft skin and glans penis.

Penile Skin Complications

Asymmetric or insufficient prepuce excision can result in a parental and patient cosmetic and social dilemma (Fig. 8.2). Excessive skin excision can result in penile torsion, chordee, and/or lateral deviation. Several techniques have been described for circumcision revision (*11*–*13*), but unlike the newborn circumcision, the former requires general anesthesia. A trapped penis can result from excessive skin removal due to a cicatricial scar. A treatment option for the trapped penis include the use of betamethasone with a 79% success in softening of the cicatrix (*14*). Surgical intervention includes vertical relaxation incision and formal repair.

Penile Trauma

Penile trauma, including urethral injury, excision of the glans and/or penile shaft, and penile necrosis, is a serious complication associated with

Fig. 8.2. Asymmetric redundant penile skin is a common complication associated with circumcision.

circumcision. Urethral injury requires a urethroplasty while excision of the glans can be repaired by suturing the excised tissue back to the penis (*15*) with usually good results if performed within 8 h. Penile necrosis can be treated by penile reconstruction and female gender reassignment with bilateral orchiectomy (*16*, *17*).

BALANITIS XEROTICA OBLITERANS

Lichen sclerosus et atrophicus or balanitis xerotica obliterans (BXO), a chronic infiltrative and cicatrizing skin condition, can result in pathological phimosis (*18*). BXO can also affect the urethra, glans, and meatus. Treatment of BXO includes medical and surgical intervention. Topical steroids of the foreskin has had limited benefit with those with minimal scar formation (*19*). Circumcision is the preferred treatment. Meatotomy or meatoplasty may be required if there is meatal involvement.

ACCESSORY URETHRAL OPENINGS

Urethral Duplication

Urethral duplication most commonly occurs in the sagittal plane with one urethra located ventrally and the other dorsally (Fig. 8.3) (*20*, *21*). Urethral duplication in the same horizontal plane, collateral urethral duplication, is very rare (*22*). The Effman classification is the most commonly used classification of urethral duplication (*23*). Anomalies have been

Fig. 8.3. Urethral duplication with catheters through meatus at the perineum and at the tip of the glans penis.

described in the genitourinary, gastrointestinal, and musculoskeletal system. The genitourinary anomalies include vesicoureteral reflux (*24*), renal agenesis, duplicated bladder, and bilateral cryptorchidism (*25*).

Children can present with a double meatus and double urinary stream (*20*, *26*, *27*), urinary incontinence, and recurrent urinary tract infections (*28*). Patient evaluation includes a voiding cystourethrogram, retrograde urethrogram, cystourethroscopy, and radiographic evaluation of the other associated anomalies. Treatment of urethral duplication is dependent on the anatomy of the urethral duplication (*24*, *28*). Surgical repair includes complete accessory tract excision since the accessory urethra should not be used as the primary urethra (*20*). Other surgical options include urethrourethrostomy of the accessory tract into the functional urethra, injection of sclerosing agents into or electrofulguration of the accessory tract, and septotomy if the septum between the two urethras is thin.

Congenital Urethral Fistula

Accessory urethral openings is a rare condition, but should be considered in a child with a history of dual urinary stream. A congenital urethrocutaneous fistula is most commonly located in the subcoronal or coronal position and is associated with a normal urethra and meatus. This abnormality can be an isolated deformity (*29*), or associated with imperforate anus or ventral chordee (*30*). Treatment is similar to repair of a urethrocutaneous fistula after hypospadias repair – circumscribe the fistula and then closure in multiple layers. However, if the glans bridge is thin, the distal urethra may need to be closed by a Thiersch-Duplay after the ventral glans is opened through the distal urethra.

PENILE MASSES

The most common penile mass in children are penile cysts. A history and physical examination are important in the evaluation of the mass. One should determine the onset of the mass, change in size and/or its appearance, and history of previous surgery.

Inclusion Cysts

Two types of inclusion cysts are commonly present on the penis. Smegma under the unretractable prepuce is the most common acquired cystic lesion of the penis. The smegma results in a yellow mass that can be soft or hard to palpation. Preputial retraction is usually not indicated since it usually retracts on its own with time. Another type of inclusion cyst is the epidermal type. Epidermal inclusion cysts may result from circumcision and other penile surgery due to islands of epithelium within the subcutaneous tissue. Excision of the cyst is usually recommended.

Parameatal Urethral Cyst

The parameatal urethral cyst, which appears as a small blister in proximity to the urethral meatus, is not a common anomaly (Fig. 8.4) (*31*). These cysts may result in urinary stream deviation. Complete excision of the cyst under anesthesia is the recommended treatment with care taken not to cause meatal stenosis.

Fig. 8.4. Parameatal urethral cyst appearing as a blister (*arrow*)

Cyst of the Median Raphe

Congenital epidermal cysts form along the median penile raphé on the penile shaft and glans, the scrotum, and the perineum (Fig. 8.5) (*32*, *33*). Unless the cysts are small and asymptomatic, excision is usually recommended.

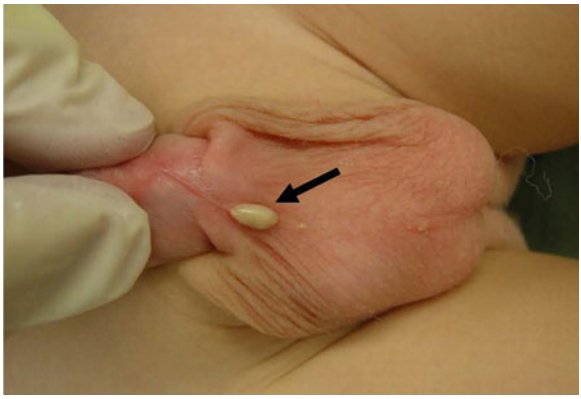

Fig. 8.5. Median raphe cyst at the penoscrotal junction (*arrow*).

Congenital Penile Nevi

Congenital penile nevi, pigmented lesions of the penile shaft and glans (Fig. 8.6), tend to be superficial and benign. The melanocytes of the lesion

Fig. 8.6. Congenital penile nevus on the penile shaft.

can be located only within the dermis, only within the dermal-epidermal junction, or within both the dermis and dermal-epidermal junction. These lesions should be excised (*34*).

ABNORMAL PENILE ORIENTATION

Penile Torsion

Penile torsion is a rotational deformity of the penile shaft (Fig. 8.7). This penile condition is usually in the counterclockwise direction (i.e., to the left side) and the penile size is normal. The orientation of the corporal bodies and the corpus spongiosum at the base of the penis are usually normal. Usually the condition is unrecognized until the foreskin is retracted or until circumcision is performed, but may be associated with hypospadias and chordee. One can suspect penile torsion on physical examination when one sees the median raphé usually spiraling obliquely around the shaft.

Fig. 8.7. Penile torsion with nearly 90-degree counter-clockwise deviation from midline. Patient also has redundant penile skin after a newborn circumcision.

Most forms of penile torsion less than 60 degrees from the midline are primarily of cosmetic significance. However, correction is typically necessary if the rotation is at least 60–90 degrees from the midline. Neonatal circumcision should be deferred if surgical repair is to be performed since it can be performed at the time of penile detorsion. In mild forms of penile torsion, rearrangement of the penile skin will usually correct the condition. The operation involves degloving the penile skin, rotating the glans in the direction opposite to the defect, and suturing the glans to the penile skin (*35*). For more severe forms of penile torsion, the base of the penis must be mobilized with the dysgenic fibrous tissue bands incised, and placing anchoring sutures at the base of the corpora cavernosa may be necessary (*36*, *37*).

Penile Curvature

Curvature of the penis (ventrally, dorsally, or laterally) may be congenital or acquired. Circumcision, other penile surgery, or trauma are secondary causes of curvature. Penile curvature can have cosmetic significance and future sexual difficulties. Penile curvature is most commonly in the ventral direction and is referred to as *chordee*. Chordee may be an isolated condition or associated with a dorsal hood of foreskin, but it is commonly associated with hypospadias (*38*). Surgical correction of ventral penile curvature most commonly involves degloving the penis with excision of fibrous tissue usually confined superficial to Buck's fascia. Dorsal placation with or without Nesbit dorsal excision and urethral reconstruction due to a short urethra may be necessary. To confirm complete chordee correction, an intraoperative artificial erection with injectable normal saline may be performed.

Congenital dorsal penile curvature may be an isolated condition, associated with a ventral hood of foreskin, and associated with epispadias. Surgical principles to repair this condition is similar to correction of chordee, but one must be careful to avoid injury to the neurovascular bundles (*39*, *40*).

Lateral penile curvature can also be congenital or acquired. This form of curvature is usually caused by hypoplasia or overgrowth of one corporal body, but postoperative scarring or asymmetric penile skin excision are common secondary causes. Surgical correction of acquired lateral penile curvature is similar to the repair of ventral and dorsal curvature.

MICROPENIS

Stretched penile length is determined by depressing the suprapubic fat pad completely and then measuring the penis from its attachment to the pubic symphysis to the tip of the glans. The two conditions that need to be differentiated when evaluating what appears to be a small penis are micropenis and inconspicuous penis. A micropenis is penis that is abnormally small while an inconspicuous penis is of normal size.

Micropenis is defined as a normally formed penis that is at least 2.5 standard deviations below the mean size in stretched length for age (*41*). However, the penile length to circumference ratio is usually normal. The scrotum is usually fused and often diminutive while the testicles are usually small and frequently cryptorchid. The penis of a full-term newborn should be at least 1.9 cm long, but the stretched penile length should be compared with standards for penile length.

Micropenis results from a deficiency of gonadotropic hormones during gestation. The etiologies of micropenis are several. The most common causes of micropenis are hypogonadotropic hypogonadism (failure of the hypothalamus to produce an adequate amount of gonadotropin-releasing hormone), hypergonadotropic hypogonadism (primary testicular failure), and idiopathic (normal hypothalamic-pituitary-testicular axis) (*42*). Also,

micropenis is often associated with chromosomal abnormalities including Klinefelter's syndrome *(47, XXY)* and trisomy involving chromosomes 8, 13, and 18 (*41*).

The initial evaluation should include a thorough medical history and a karyotype at birth. Consultation by a pediatric endocrinologist is also usually obtained to assist in determining the etiology and evaluating for other abnormalities. Further description of the evaluation and management is beyond the purpose of this textbook.

INCONSPICUOUS PENIS

An inconspicuous penis refers to a penis with a normal stretched penile length and normal diameter of the penile shaft that appears to be small (*43*). There are several forms of acquired and congenital inconspicuous penis, including trapped penis, buried penis, and webbed penis (*44*).

Buried Penis

A buried penis is a normally developed penis that is hidden by the suprapubic fat pad. A buried penis, also known as concealed and hidden penis (*45*), can be classified into three categories (*46*, *47*): (*1*) obesity hiding the penis; (*2*) poor penopubic fixation of the skin at the penile base; and (*3*) trapped penis from cicatricial scarring after a circumcision or other penile surgery.

The congenital form of buried penis is believed to be due to the inelasticity of the dartos fascia and restricted extension of the penis resulting from the penile skin not being attached to the deep fascia (Fig. 8.8). There are several causes of the acquired form, including obesity hiding the penis due to abundant fat on the abdominal wall, and a trapped penis due to embedding of the penis in the suprapubic fat pad from scar formation over the glans. The latter cause may result from routine circumcision in a baby with a webbed penis. Also, this may result from circumcision in children whose penile shaft retracts naturally into the scrotum due to the penile skin at the base forming a cicatrix over the retracted phallus (Fig. 8.9). This condition is different from the transient buried penis resulting from a large suprapubic fat pad seen in early childhood (*48*). The congenital and acquired forms can increase the incidence of difficulty voiding, balanitis, proper hygiene, and propensity for urinary tract infections (*49*).

The treatment options for children with buried penis are dependent upon the cause of the condition. Patients with buried penis secondary to obesity should be referred back to the primary care provider for an exercise and weight loss program to be implemented prior to considering surgical intervention. Children with secondary cicatricial scarring after penile surgery can be managed with the combination of topical betamethasone and manual retraction (*14*) or forceful dilation of the cicatrix with a fine hemostat

Fig. 8.8. Buried penis (**a**), which may be visualized by retraction of the skin lateral to the penile shaft (**b**).

Fig. 8.9. A trapped penis resulting from a cicatricial scarring resulting from a newborn circumcision.

in the office. If these interventions are not successful, then correction under general anesthesia is necessary. The surgical technique is similar to that used to correct the congenital buried penis.

A number of surgical techniques have been described to correct the buried penis (*46*, *47*, *50*). In moderately severe cases, the dysgenic bands of tissue should be removed. This band is usually located on the dorsal surface of the penile shaft. The scrotal subcutaneous tissue should be fixed to the ventral

aspect of the penile base and the penile shaft subcutaneous tissue should be fixed to the pubic fascia. Skin coverage of the penis can be provided by several techniques. One technique involves unfurling the foreskin and using it for ventral skin coverage. Penoscrotal Z-plasty, island pedicle of ventral preputial skin, lateral penile shaft Z-plasty, or skin graft coverage can also be used for skin coverage. In the most severe cases, the suspensory ligament of the penis can be divided and the suprapubic fat excised or liposuctioned (*46*, *51*). Since prepubertal boys may lose their fat pad with growth, liposuction should be reserved for adolescent boys.

Webbed Penis

Webbed penis is a acquired or congenital condition resulting from the scrotal skin extending onto the ventral aspect of the penis. This condition is also referred to as penoscrotal fusion. Circumcision and other penile surgery are causes of the acquired condition resulting from excessive removal of ventral penile skin. An abnormality of the attachment between the scrotum and penis result in the congenital form.

Several surgical techniques have been developed to repair the webbed penis. One technique involves the fixation of the ventral penile shaft to the scrotal subcutaneous tissue (*52*). Another technique, which can be performed separately in combination with the previous technique, involves the incision of the web transversely and closure of the skin vertically. Skin coverage techniques are similar to those used in the repair of the buried penis.

PRIAPISM

Priapism is a condition not only affecting the adult male, but also in the pediatric population. Priapism, which is commonly painful, is a prolonged penile erection that is sustained for greater than 4 h with the absence of stimulation. Priapism can be categorized into three types: (*1*) Ischemic (veno-occlusive, low-flow); (*2*) stuttering (intermittent) priapism; and (*3*) nonischemic (arterial, high-flow).

Ischemic priapism is characterized by minimal or no cavernous blood flow with hypoxic, acidotic, and hypercapnic cavernous blood gases. The corpora are rigid and tender to palpation. This form of priapism is most commonly secondary to homozygous sickle cell disease, but is also seen in children with leukemia and other malignancies (*53*, *54*). Sickle cell disease results in priapism due to red blood cell sickling within the corpora cavernosa during normal erection, resulting in venous stasis and a low-flow state. The ischemia that results causes pain.

Conservative treatment with hydration, oxygenation, analgesia, alkalization, and transfusion with the goal of reducing hemoglobin S concentration is the initial treatment of low-flow priapism resulting from sickle cell disease

(*55*–*57*). Concurrent therapy includes evacuation of blood and irrigation of the corpora cavernosa along with intracavernous injections of α-adrenergic sympathomimetic agents (*58*). More invasive intervention of surgery to allow corporal drainage by shunt procedures may be necessary if there is a lack of response to medical therapy (*57*, *59*, *60*).

Stuttering (intermittent) priapism, a recurrent form of ischemic priapism, lasts less than 2 h with intervening periods of detumescence and is painful. This type of priapism is more common than prolonged erections in the sickle cell patient. Pseudoephedrine at bedtime can be used to treat stuttering priapism.

Nonischemic priapism, caused by unregulated cavernous arterial inflow, results in the penis being neither fully rigid nor painful. A cavernous artery–corpora cavernosa fistula, resulting in this form of priapism, usually results from trauma (e.g., perineal trauma, such as a straddle injury). Corporal irrigation is diagnostic with the aspirated blood bright red and similar to arterial blood on blood gas. The fistula is usually demonstrated on color Doppler ultrasonography. Since spontaneous resolution may occur, the initial management is observation (*58*) with superselective embolization of penile and cavernous arteries (*58*, *61*–*63*) if this fails.

SCROTAL ANOMALIES

Penoscrotal Transposition

Penoscrotal transposition may be partial or complete. Terms used to describe less severe forms include bifid scrotum and scrotal engulfment. Penoscrotal transposition is frequently associated with proximal hypospadias with chordee (*64*), sex chromosome abnormalities (*65*), and caudal regression (*66*). There is a high association of complete penoscrotal transposition and a normal scrotum with urinary tract abnormality, including renal dysplasia and agenesis (*67*, *68*). Renal ultrasonography and voiding cystourethrography are recommended in these latter children.

The steps of surgical repair, which is commonly performed during hypospadias repair, involve separating and freeing the penis from the scrotum and moving the penis superiorly while relocating the scrotum to a dependent position (*69*–*71*).

Scrotal Hypoplasia

The underdevelopment of one or both sides of the scrotum is referred to as scrotal hypoplasia. This condition most commonly occurs in association with undescended testicles and in infants with ambiguous genitalia. An orchiopexy for the child with an undescended testicle can correct the former etiology while genital reconstruction may be required in the latter condition.

Bifid Scrotum

Bifid scrotum, most often associated with proximal hypospadias, is when there is a complete separation of the labioscrotal folds without a median raphé. The techniques used to correct this condition is similar to those used for repair of penoscrotal transposition, and is usually performed during hypospadias repair.

REFERENCES

1. Johnson P, Maxwell D. Fetal penile length. Ultrasound Obstet Gynecol 2000;15: 408–410.
2. Zalel Y, Pinhas-Hamiel O, Lipitz S, et al. The development of the fetal penis—an in utero sonographic evaluation. Ultrasound Obstet Gynecol 2001;17:129–131.
3. Oster J. Further fate of the foreskin: Incidence of preputial adhesions, phimosis, and smegma among Danish schoolboys. Arch Dis Child 1968;43:200–203.
4. Kayaba H, Tamura H, Kitajima S, et al. Analysis of shape and retractability of the prepuce in 603 Japanese boys. J Urol 1996;156:1813–1815.
5. Palmer LS, Palmer JS. The efficacy of topical betamethasone for treating phimosis: a comparison of two treatment regimens. Urology 2008;72:68–71.
6. Palmer JS (editor): An international view on circumcision. Dialogues in Pediatric Urology 2009;30(6):1–8.
7. Hardwick-Smith S, Mastrobattista JM, Wallace PA, Ritchey ML. Ring block for neonatal circumcision. Obstet Gynecol 1998;91:930–934.
8. Baskin LS, Canning DA, Snyder HM, Duckett J. Treating complications of circumcision. Pediatric Emergency Care 1996;12:62–68.
9. Ben Chaim J, Livne PM, Binyamini J, et al. Complications of circumcision in Israel: A one year multicenter survey. Isr Med Assoc J 2005;7:368–370.
10. Litvak AS, Morris JA Jr, McRoberts JW. Normal size of the urethral meatus in boys. J Urol 1976;115:736–737.
11. Brisson PA, Patel HI, Feins NR. Revision of circumcision in children: report of 56 cases. J Pediatr Surg 2002;37:1343–1346.
12. Redman JF. Circumcision revision in prepubertal boys: analysis of a 2-year experience and description of a technique. J Urol 1995;153:180–182.
13. Ching, CB and Palmer JS. Circumcision revision for asymmetric redundant skin resulting in minimal suture lines. Can J Urol 2008;15:4304.
14. Palmer JS, Elder JS, Palmer LS. The use of betamethasone to manage the trapped penis following newborn circumcision. J Urol 2005;174:1577–1578.
15. Sherman J, Borer JG, Horowitz M, Glassberg KI. Circumcision: Successful glanular reconstruction and survival following traumatic amputation. J Urol 1996;156: 842–844.
16. Gearhart PJ, Rock JA. Total ablation of the penis after circumcision with Electrocautery. A method of management and long-term followup. J Urol 1989;142: 799–801.
17. Bradley SJ, Oliver GD, Chernick AB, Zucker KJ. Experiment of nurture: Ablatio penis at 2 months, sex reassignment at 7 months, and a psychosexual follow-up in young adulthood. Pediatrics 1998;102:E9.
18. Chalmers RJ, Burton PA, Bennett RF, et al. Lichen sclerosus et atrophicus. A common and distinctive cause of phimosis in boys. Arch Dermatol 1984;120:1025–1027.
19. Vincent MV and Mackinnon E. The response of clinical balanitis xerotical obliterans to the application of topical steroid-based creams. J Pediatra Surg 2005;40:709–712.
20. Salle JLP, Sibai H, Rosenstein D, et al. Urethral duplication in the male: review of 16 cases. J Urol 2000;163:1936–1940.
21. Slavov C, Donkov I, Popov E. Case of duplicated urethra in an adult male presenting with symptoms of bladder outlet obstruction. Eur Urol 2007;52:1249–1251.

22. Ching CB and Palmer JS. Collateral urethral duplication. Dialogues in Pediatric Urology 2008;29(3):16–17.
23. Effman EL, Lebowitz RL, Colodny AH. Duplication of the urethra. Pediatric Radiology April 1976;119:179–185.
24. Podesta ML, Medel R, Castera R, et al. Urethral duplication in children: surgical treatment and results. J Urol 1998;160:1830–1833.
25. Woodhouse CRJ, Williams DI. Duplications of the lower urinary tract in children. British J Urol 1979;51:481–487.
26. Kennedy HA, Steidle CP, Mitchell ME, et al. Collateral urethral duplication in the frontal plane. J Urol 1988;139:332–334.
27. Urakami S, Igawa M, Shiina H, et al. Congenital collateral urethral duplication in the frontal plane. J Urol 1999;162:2097–2098.
28. Farrell RWR, Sparnon AL. Complete epispadiac urethral duplication. J Pediatr Surg 1987;22(2):175–176.
29. Tennenbaum SY and Palmer LS. Congenital urethrocutaneous fistulas. Urology 1994;43:98–99.
30. Ritchey ML, Sinha A, Argueso L. Congenital fistula of the penile urethra. J Urol 1994;151:1061–1062.
31. Shiraki IW. Parameatal cysts of the glans penis: A report of 9 cases. J Urol 1975;114:544–548.
32. Little LS Jr, Keating MA, Rink RC. Median raphe cysts of the genitalia. J Urol 1992;148:1872–1873.
33. Krauel L, Tarrado X, Garcia-Aparicio L, Lerena J, et al. Urology 2008;71: 830–831.
34. Papali AC, Alpert SA, Edmondson JD, Maizels M, et al. A review of pediatric glans malformations: a handy clinical reference. J Urol 2008;180:1737–1742.
35. Bar-Yosef Y, Binyamini J, Matzkin H, Ben-Chaim J. Degloving and realignment—simple repair of isolated penile torsion. J Urol 2007;69:369–371.
36. Pomerantz P, Hanna M, Levitt S, et al. Isolated tosion of the penis: report of six cases. Urology 1978;11:37–39.
37. Slawin KM, Nagler HM. Treatment of congenital penile curvature with penile torsion: a new twist. J Urol 1992;14:152–154.
38. Cendron J, Melin Y: Congenital curvature of the penis without hypospadias. Urol Clin North Am 1981;8:389–395.
39. Baskin LS. Fetal genital anatomy reconstructive implications. J Urol 1999;162:527–529.
40. Baskin LS, Erol A, Li YW, Liu WH. Anatomy of the neurovascular bundle: Is safe mobilization possible? J Urol 2000;164:977–980.
41. Aaronson IA. Micropenis: Medical and surgical implications. J Urol 1994;152:4–14.
42. Lee PA, Mazur T, Danish R, et al. Micropenis: I. Criteria, etiologies and classification. Johns Hopkins Med J 1980;146:156–163.
43. Bergeson PS, Hopkin RJ, Bailey RB Jr, et al. The inconspicuous penis. Pediatrics 1993;92:794–799.
44. Palmer LS, Kogan SJ. The small and buried penis. Adv Urol 1995;8:225–247.
45. Cromie WJ, Ritchey ML, Smith RC, Zagaja GP. Anatomical alignment for correction of buried penis. J Urol 1998;160:1482–1484.
46. Maizels M, Zaontz M, Donovan J, et al. Surgical correction of the buried penis: Description of a classification system and a technique to correct the disorder. J Urol 1986;136:268–271.
47. Casale AJ, Beck SD, Cain MP, et al. Concealed penis in childhood: A spectrum of etiology and treatment. J Urol 1999;162:1165–1168.
48. Eroglu E, Bastian OW, Ozkan HC, Yorukalp OE, Goksel AK. Buried penis after newborn circumcision. J Urol 2009;181:1841–1843.
49. Kon M. A rare complication following circumcision: the concealed penis. J Urol 1983;130:573–574.
50. Karapetian A, Palmer JS. Repair of the buried penis: 3-point technique. J Am Coll Surg 2007; 205(suppl 3):S104.

51. Shenoy MU, Srinivasan J, Sully L, Rance CH. Buried penis: Surgical correction using liposuction and realignment of skin. BJU Int 2000;86:527–530.
52. Palmer JS: 2-point repair of the webbed penis (personal communication, 2010).
53. Dewan PA, Tan HL, Auldist AW, Moss DI. Priapism in childhood. Br J Urol 1989;64:541–545.
54. Friedman J. Priapism: an unusual presentation of appendicitis. Pediatr Emerg Care 1998;14:143–144.
55. Seeler RA. Intensive transfusion therapy for priapism in boys with sickle cell anemia. J Urol 1973;110:360–361.
56. Hamre MR, Harmon EP, Kirkpatrick DV et al. Priapism as a complication of sickle cell disease. J Urol 1991;145: 1–5.
57. Miller ST, Rao SP, Dunn EK, Glassberg KI. Priapism in children with sickle cell disease. J Urol 1995;154:844–847.
58. Montague DK, Jarow J, Broderick GA, et al. American Urological Association guideline on the management of priapism. J Urol 2003;170:1318–1324.
59. Tarry WF, Duckett JW, Snyder HM. Urological complications of sickle cell disease in a pediatric population. J Urol 1987;138: 592–594.
60. Chakrabarty A, Upadhyay J, Dhabuwala CB, et al. Priapism associated with sickle cell hemoglobinopathy in children: Long-term effects on potency. J Urol 1996;155: 1419–1423.
61. Callewaert P, Stockx L, Bogaert G, Baert L. Post-tramatic high-flow priapism in a 6 year old boy: management by percutaneous placement of bilateral vascular coils. Urol 1998;52:134–137.
62. Volkmer BG, Nesslauer T, Kraemer SC, et al. Prepubertal high flow priapism: Incidence, diagnosis and treatment. J Urol 2001;166:1018–1022.
63. Kuefer R, Bartsch G Jr, Herkommer K, et al. Changing diagnostic and therapeutic concepts in high-flow priapism. Int J Impot Res 2005;17:109–113.
64. Pinke LA, Rathbun SR, Husmann DA, Kramer SA. Penoscrotal transposition: Review of 53 patients. J Urol 2001;166:1865–1868.
65. Yamaguchi T, Hamasuna R, Hasui Y, et al. 47,XXY/48,XXY, +21 chromosomal mosaicism presenting as hypospadias with scrotal transposition. J Urol 1989;142: 797–798.
66. Lage JM, Driscoll SG, Bieber FR, et al. Transposition of the external genitalia associated with caudal regression. J Urol 1987;138:387–389.
67. MacKenzie J, Chitayat D, McLorie G, et al. Penoscrotal transposition: a case report and review. Am J Med Genet 1994;49:103–107.
68. Parida SK, Hall BD, Barton L, et al. Penoscrotal transposition and associated anomalies: report of five new cases and review of the literature. Am J Med Genet 1995;59:68–75.
69. Glenn JF, Anderson EE. Surgical correction of incomplete penoscrotal transposition. J Urol 1973;110:603–5.
70. Ehrlich RP, Scardino PT. Surgical correction of scrotal transposition and perineal hypospadias. J Pediatr Surg 1982;17:175–177.
71. Levy JB, Darson MF, Bite U. Modified pudendal-thigh flap for correction of penoscrotal transposition. Urology 1997;15:597–600.

9 Hypospadias

Warren T. Snodgrass

Abstract Hypospadias is considered the result of arrested development, leaving incomplete urethral formation sometimes associated with ventral penile curvature. The minority of cases occurring with other syndromes, or when there is also undescended testis, warrant a preoperative karyotype to detect intersex disorders. Otherwise the only preoperative evaluation needed is assessment of glans size, as there may be benefit from preoperative testosterone therapy to increase glans diameter, usually in proximal hypospadias. Today most primary cases are corrected by tubularizing the urethral plate – tissue that should have originally created the urethra when development stopped. Prepucial flaps remain an option for repair, as do planned 2-stage flap or graft procedures. The majority of hypospadias complications relate to urethroplasty, most commonly including fistulas, obstruction to the neourethra (by meatal stenosis or urethral stricture), or wound dehiscence. Incidence varies by technique used and extent of the hypospadias defect (distal versus proximal). Reoperative urethroplasty can be accomplished using similar methods as for primary surgery, but complication rates are greater. At times excision of scarred tissues with planned 2-stage graft repairs is required to re-create a neourethral plate to subsequently tubularize.

Keywords Hypospadias · Urethroplasty · Ventral curvature · TIP · Inlay graft · Staged buccal graft

INTRODUCTION

Hypospadias is the second most common birth defect in males, potentially affecting both urinary and sexual function of the penis. Correction is surgical, and it is commonly stated over 200 operations are described for urethroplasty. New understanding of the anatomy of hypospadias during the last 20 years has led to changes in both means for straightening associated ventral curvature and performing urethroplasty, while also improving cosmetic outcomes. Today pediatric urologists are much nearer the goal of

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correcting hypospadias by creating a penis with satisfactory function and normal appearance. This chapter reviews current aspects in diagnosis and management of hypospadias for the general urologist.

ETIOLOGY

Incomplete fusion of the urethral folds is considered the underlying cause for hypospadias. The key period for the indifferent genital tubercle to masculinize is from the 9th to 12th gestational week. Testosterone from the fetal testes stimulates closure of the urethral folds through conversion by 5 alpha reductase II to dihydrotestosterone, which then binds to androgen receptors to initiate a cascade of down-stream effects.

Formation of the prepuce lags behind urethral development, and is not completed until the 20th week.

Hypospadias represents arrested penile development. Consequently, the urethral opening can occur from the perineum, where fusion of urethral folds begins, to the proximal glans near the point this fusion normally is completed. The epithelial strip extending from the meatus to the tip of the glans is referred to as the urethral plate, representing tissues that should have completed urethral tubularization. The glans does not fuse ventrally under the meatus, resulting in two "wings" to either side of the urethral plate. Along the shaft, the corpus spongiosum diverges along the lateral margins of the urethral plate to join ipsilateral glans wings. Typically, there is no frenulum, and ventral prepucial development is incomplete whereas the dorsal aspect is formed, creating a dorsal hood. Ventral curvature of the penis may be noted, especially with more proximal hypospadias.

Defects in the hormonal processes of masculinization have long been implicated in hypospadias. Various studies have reported abnormalities in each of the basic steps in testosterone production and action, but generally such defects are found in less than 10% of patients. An increased risk following in vitro fertilization has been reported, and is thought due to progesterone administered early in these pregnancies. Increasing incidence of the condition has been attributed to environmental estrogens and progesterones or other disruptive factors. Low birth weight, twins, and maternal age greater than 35 years are associated with increased likelihood for hypospadias. Genetic factors are implicated by the observation that the likelihood a boy will have hypospadias increases to approximately 10% if father or sibling is affected.

INCIDENCE

Hypospadias occurs in approximately 0.7% of males. Prior to the 1970s data from several sources agreed the defect occurred in 1 of 300 boys; however, subsequent reports from both Europe and the US indicate a doubling of this rate to 1 in 150.

ASSOCIATED CONDITIONS

The majority of boys with hypospadias have no other associated anomalies. Cryptorchidism reportedly occurs in approximately 5% of distal and up to 32% of proximal cases.

The finding of both hypospadias and cryptorchidism indicates possible intersexuality, warranting a karyotype. Intersex conditions occur in approximately 15% of these patients, increasing to 50% if at least one testis is not palpable (*1*). Most common findings are mixed gonadal dysgenesis or true hermaphroditism (ovatesticular disorders of sexual differentiation).

Hypospadias also occurs in various syndromes, often associated with cryptorchidism.

DIAGNOSIS

In most cases the diagnosis is readily determined by inspection of the penis, with attention called to the anomaly in the newborn nursery by the incomplete prepuce. However, not all boys with a hooded foreskin have hypospadias, as the urethral meatus can be normally positioned despite an incomplete prepuce. Boys with hypospadias occasionally also have torsion of the penis, most often twisted toward the left. Penoscrotal transposition may be noted, especially with proximal shaft to perineal hypospadias.

A variant of distal hypospadias termed the megameatus intact prepuce (MIP) presents with a normal foreskin, and so may not be detected until circumcision is performed or the skin becomes retractable. Past authors describing this entity stressed practitioners performing circumcision needed to be wary of concealed hypospadias, resulting in some newborn circumcisions being stopped only to subsequently discover a normal urinary meatus. However, prepuce is not needed for urethroplasty in these patients and so newborn and intraoperative circumcisions can be completed despite finding unexpected concealed hypospadias (*2*), with the patient subsequently referred to a pediatric urologist for urethroplasty.

PREOPERATIVE EVALUATION

Because hypospadias most often is an isolated anomaly, the majority of patients need no investigation beyond confirmation of the defect on physical examination. As mentioned above, the additional finding of cryptorchidism should prompt karyotyping. Imaging of the kidneys is not necessary since disordered penile development begins after renal formation. Similarly, lower tract imaging is also unnecessary, even in proximal cases where the most common finding is an enlarged prostatic utricle that rarely has clinical significance.

INDICATIONS FOR SURGERY

Hypospadias can result in an abnormal urinary stream, while ventral curvature can impair intromission and a proximal meatus can prevent normal semen deposition. The abnormal foreskin found in most cases also calls attention to the anomaly since the penis appears neither natural nor circumcised.

Normal voiding depends upon fusion of the glans over the urethra to direct the stream forward and focus it without lateral spaying. Urethral defects proximal to the glans cause difficulties aiming the stream and increase the likelihood of spraying. Glanular hypospadias with separated glans wings is likely to result in similar voiding disturbances, while those cases with fusion of at least 2 mm of glans proximal to the meatus should be able to void satisfactorily without urethroplasty.

Ventral curvature is found in approximately 15% of boys with distal forms of hypospadias, and in over 50% of those with the meatus on the proximal penile shaft or in the scrotum or perineum. Bending in distal cases most often is less than 30 degrees and will not prevent intercourse, whereas curvature greater than 30 degrees more often found in proximal cases may preclude penetration.

Proximal cases additionally may have deep midline clefts in the scrotum and/or transposition of the scrotum higher than usual alongside the penile shaft. These findings combine with downward curvature of the penis to create a feminized appearance to the external genitalia.

Given these concerns and modern outcomes of surgical correction, urethroplasty is recommended for all but those glanular cases with adequate glans fusion. Circumcision or foreskin reconstruction is indicated for the foreskin anomaly in boys with hypospadias and those with isolated hooded prepuce.

PREOPERATIVE HORMONE STIMULATION

No study confirms benefits of preoperative androgen therapy before hypospadias repair. Use has been advocated for the small appearing penis and/or glans, to potentially reduce ventral curvature, and to improve vascularity to skin before reoperations. Of these, the most common reason for androgen stimulation is to increase the size of the penis, and studies document at least temporary penile growth and increase in glans circumference (*3*).

Both topical and parenteral testosterone therapy have been used, with no apparent advantage to either route of administration. Parenteral regimens utilize testosterone enanthate 2 mg/kg given IM 5 and 2 weeks preoperatively, or every 3–4 weeks for three injections. Testosterone enanthate 2 mg/kg/wk can be administered topically twice daily for 3 weeks.

TIMING OF SURGERY

A report from the American Academy of Pediatrics in 1996 (*4*) suggested the optimal time for elective male genital surgery is between 6 and 12 months. However, significant phallic growth is apparent in most infants by 3 months, presumably due to the postnatal testosterone surge that peaks around the 2nd month. Furthermore, from an anesthetic perspective, day surgery is safely accomplished after the 50th gestational week (*5*). Consequently, hypospadias repair can be scheduled in healthy term babies at 3 months, which may confer a benefit in that there often is less peripenile fat between 3 and 6 months than between 6 and 12 months.

SURGICAL REPAIR

During the past 15 years the number of different procedures performed for various extents of hypospadias had diminished considerably, and a current algorithm for decision-making is shown in Fig. 9.1.

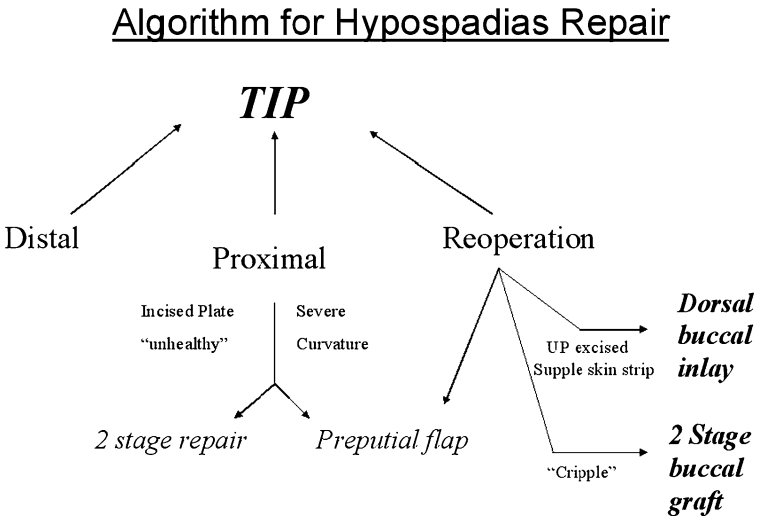

Fig. 9.1. Algorithm for hypospadias repair.

Distal Hypospadias

A recent survey of pediatric urologists indicated the most commonly used technique for distal repairs is TIP (*6*). This procedure involves tubularization of the urethral plate facilitated by midline incision to achieve a satisfactory neourethra caliber without skin flaps (Fig. 9.2). Since flaps are not used the prepucial hood can either be removed by circumcision or ventrally approximated for foreskin reconstruction according to family preference (*7*).

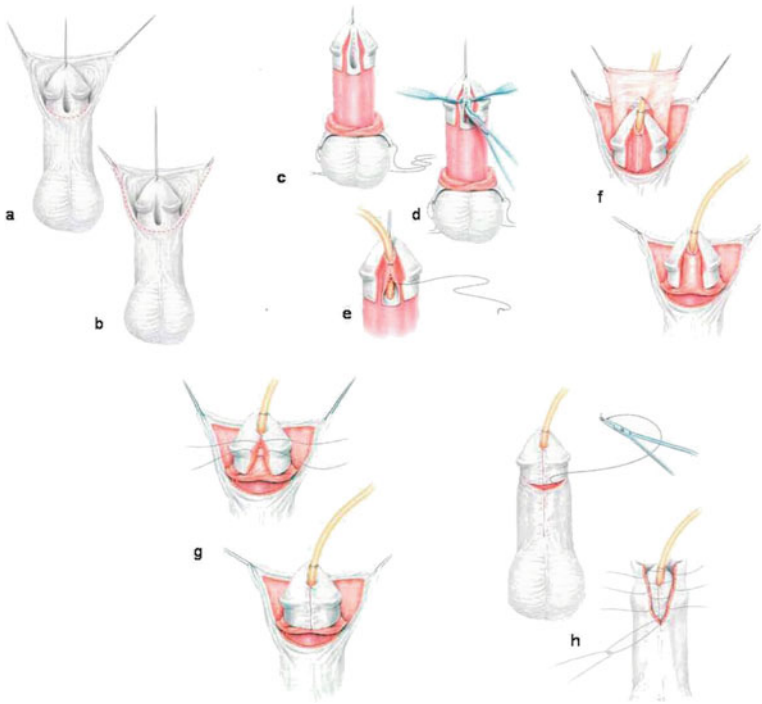

Fig. 9.2. Distal Repair. **a**: Skin incision for circumcision. **b**: Skin incision for foreskin reconstruction. **c**: Glans wings separated from urethral plate. **d**: Incising the urethral plate. **e**: Urethral plate tubularized over stent. **f**: Dartos pedicle brought ventrally to cover neourethra. **g**: Glansplasty beginning at neomeatus. **h**: Skin coverage completed with circumcision or foreskin reconstruction.

A urethral stent diverts urine into diapers for approximately 1 week after surgery.

Unlike prior techniques such as meatoplasty and glansplasty (MAGPI) or flip-flap, TIP can be used without concern for specific anatomic variations in the meatus and urethral plate (*8*). Of available procedures it most reliably creates a vertical, slit meatus and normal appearing glans.

Proximal Hypospadias

TIP can also be used to correct midshaft hypospadias and many cases with more proximal defects (Fig. 9.3). The main contraindication is ventral curvature resulting in urethral plate transection to facilitate straightening. In a series of consecutive patients all with midshaft and approximately two-thirds with proximal shaft to perineal hypospadias were corrected by TIP, while the remainder with proximal defects had urethral plate transection. The main alternative to TIP when the urethral plate is maintained is onlay flap (Fig. 9.4), but if the plate is transected either a 1-stage tubularized

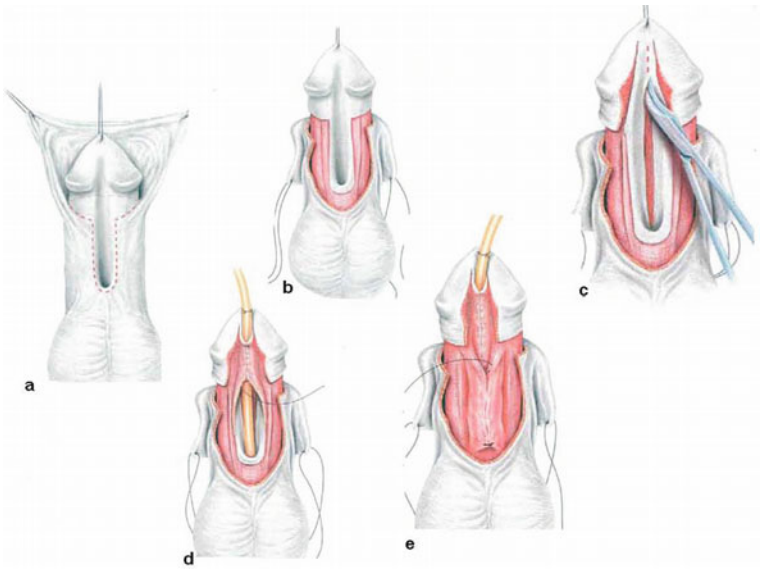

Fig. 9.3. TIP for proximal hypospadias. **a**, **b**: Skin incision preserves urethral plate. **c**: Midline incision of urethral plate. **d**: Tubularization of urethral plate. **e**: Spongioplasty approximates corpus spongiosum over neourethra before a dartos or tunica vaginalis barrier flap is added.

prepucial flap (Fig. 9.5) or 2-stage flap (Fig. 9.6) or graft urethroplasty is required.

Because the penis and scrotum derive from different embryologic sources scrotoplasty to correct midline clefts and penoscrotal transposition can be performed during hypospadias repair without vascular compromise to either structure.

Correcting Penile Curvature

Although corporal disproportion was implicated in the etiology of curvature near the beginning of hypospadias surgery, the prevailing theory held that fibrous bands of dartos and corpus spongiosum tethered the penis ventrally. Straightening was achieved by excising these "chordee" tissues, which included what is now termed the urethral plate. However, a number of embryonic and histologic studies have challenged this view, and today it is widely accepted the penis is bent due to arrested development rather than from abnormal tissues.

When the penis develops with curvature, all tissues on the ventral aspect may be relatively shortened, including shaft skin, dartos, corpus spongiosum, urethral plate, and corpus cavernosa. Most apparent curvature resolves when the shaft skin is released during degloving, sometimes facilitated by excision of dartos. While excision of the corpus spongiosum and urethral

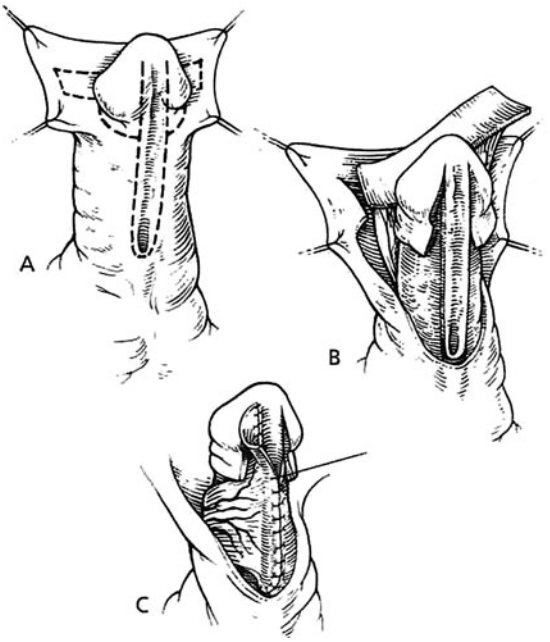

Fig. 9.4. Onlay preputial flap. **a**, **b**: A rectangular flap of appropriate length and a width of approximately 8–10 mm is cut from the inner prepuce, maintaining its blood supply. **c**: The flap is rotated ventrally and sutured to the urethral plate. The pedicle of the flap is used to cover the neourethral suture lines.

plate may also lessen curvature, in most cases some extent of curvature persists due to corpora cavernosa disproportion (*9*).

Bending less than 30 degrees can be readily straightened by midline dorsal plication popularized by Baskin (*10*). Typically curvature greater than 30 degrees after degloving and excision of dartos has led to transection of the urethral plate with subsequent ventral corporal grafting. However, the plate can instead be elevated from the underlying corpora and grafting then performed while maintaining the plate for urethroplasty (*11*). Dissection to release the urethral plate can also be continued along the proximal formed urethra to the bulb to facilitate penile straightening without transecting the plate (*12*).

COMPLICATIONS

Most complications after hypospadias repair result from urethroplasty. Less common is recurrent ventral curvature. Problems related to skin closure generally have received the least attention. While there is some variation in complication rates among various surgical techniques, generally the likelihood of problems is best predicted by severity of hypospadias

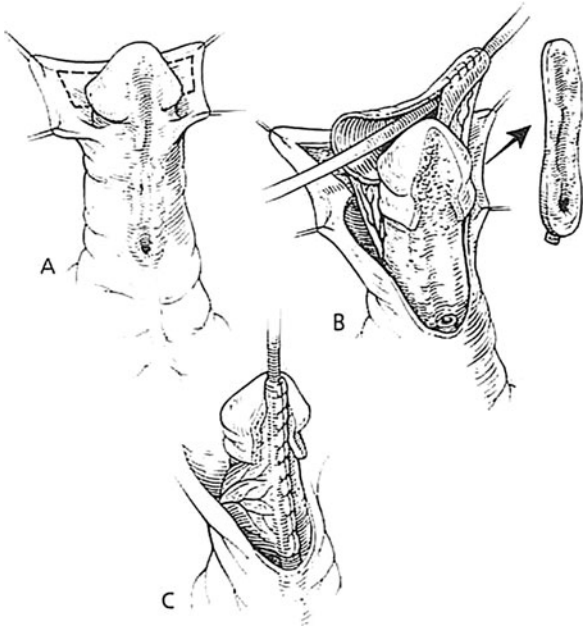

Fig. 9.5. Tubularized preputial flap. **a**: A rectangular flap of appropriate length approximately 14 mm wide can be harvested from the inner prepuce. **b**: Following resection of the urethral plate, the flap is mobilized and then tubularized over a stent. **c**: The neourethra is rotated ventrally, placing the suture line against the corpora cavernosa.

corrected. It should also be noted that the presence of any complication should prompt search for additional problems, for example, patients with fistulas need to also be evaluated for distal obstruction and diverticulum. Most complications require further surgery to correct, which typically is delayed for 6 months or longer to allow tissue reaction from earlier surgery to subside.

Fistulas

The most common problem after hypospadias urethroplasty is urethrocutaneous fistula. While the cause is uncertain, overlapping suture lines between urethroplasty and skin closure is widely believed a contributing factor. Steps thought to decrease risk for fistula development include subepithelial sutures to turn epithelial edges into the neourethra, 2-layer urethroplasty, and interposition of tissue flaps, including dartos, corpus spongiosum, and/or tunica vaginalis, between the neourethra and shaft skin closures.

During fistula repair meatal stenosis and urethral stricture have to be excluded as causative factors. Diverticulum may also be associated with increased risk for fistula. Patients with a single fistula may have additional leaks discovered when the neourethra is distended with fluid

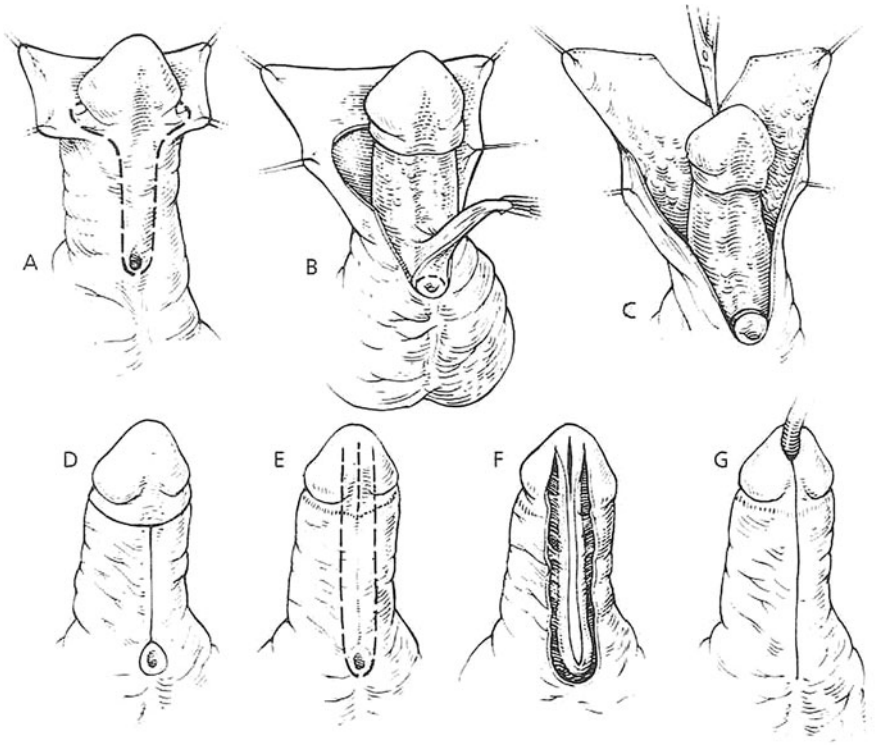

Fig. 9.6. Two-stage hypospadias repair. **a**: The initial U-shaped skin incision preserves the urethral plate. **b**: Removal of the shaft portion of the urethral plate. **c**: Prepuce is incised dorsally to rotate skin to the ventrum. **d**: The first stage is completed using subcuticular stitches. **e**: Lines of incision for the second stage. The glanular incisions are the same as those used in distal TIP urethroplasty, with the outer incisions separating the glans wings from the urethral plate while the midline relaxing incision widens the plate. **f**: The incisions are completed and the neourethra will next be tubularized over a stent. **g**: The completed repair.

intraoperatively. Repair involves excision of the fistula tract, subepithelial closure of the hole in the urethra, and coverage of the defect with a tissue flap.

A special situation involves fistulas at the coronal margin. Those occurring with only a thin bridge of tissue holding the glans wings together require reoperative urethroplasty/glansplasty, whereas those with more solid glans wings fusion can undergo routine fistula repair.

Meatal Stenosis

Meatal stenosis may result from technical errors, such as tubularizing the neourethra too far distally, or from vascular compromise. These usually result in early detection of stranguria within a few months of surgery.

Late presentation a year or more after apparently successful repair raises concern for balanitis xerotica obliterans (BXO), especially if the meatus has a white discoloration. Meatal stenosis may best be corrected by excision of scarred tissues with staged graft urethroplasty, and this approach using buccal mucosa is required when BXO is diagnosed.

Urethral Stricture

Neourethral strictures most commonly occur at the proximal anastomosis to the native urethra, especially when tubularized prepucial flaps are used. They may also develop subcoronally. Uroflowometry typically will demonstrate a peak flow less than 5 cc/s with a plateau-shaped curve, and the diagnosis is confirmed by endoscopy. Urethrography can be considered, but a catheter may be difficult to pass after skin flap urethroplasty; even in the absence of obstruction.

Anastomotic strictures may be very short diaphragms less than 2 mm in length, and these warrant a single attempt at correction by optical urethrostomy. Recurrent or longer strictures may best be repaired using single stage dorsal inlay grafts.

Urethral Diverticulum

Ballooning of the neourethra may indicate too large a skin flap was used in urethroplasty, or distal obstruction. Even when excessive skin was not used and distal obstruction is not found, the normal resistance to urine flow that results in glans envelopment of the distal urethra can prompt expansion of prepucial flaps to create a diverticulum.

Excision of the excessive skin corrects the defect, and recurrences are unusual.

Wound Dehiscence

Partial or complete wound disruption may occur after hypospadias repair and usually is noted when the patient returns for removal of the urethral catheter. Potential causes for dehiscence include tension on suture lines, use of rapidly dissolving sutures such as chromic catgut, and use of a large urethral catheter. Most often there is no apparent reason for glans dehiscence. Reoperation is performed 6 months later.

HYPOSPADIAS REOPERATIONS

Techniques for primary hypospadias repair have also been used for reoperations, although complication rates are consistently increased, presumably due to impaired tissue vascularity after prior operation.

Tip

TIP reoperation has been reported most often after 1–2 failed prior surgeries, and it probably should not be considered if the urethral plate appears grossly scarred. Incidence of fistulas increases if a tissue barrier flap is not placed over the neourethra (*13*). Complication rates average approximately 20%.

Inlay Grafting

If a healthy appearing skin strip can be maintained in reoperations, midline incision as with TIP can be used to widen it and the resultant defect filled with a skin or buccal mucosal graft (Fig. 9.7). The neourethra is then tubularized and covered with a barrier layer for single stage repair (*14*). This technique should not be used when there is suspicion of BXO in the urethra.

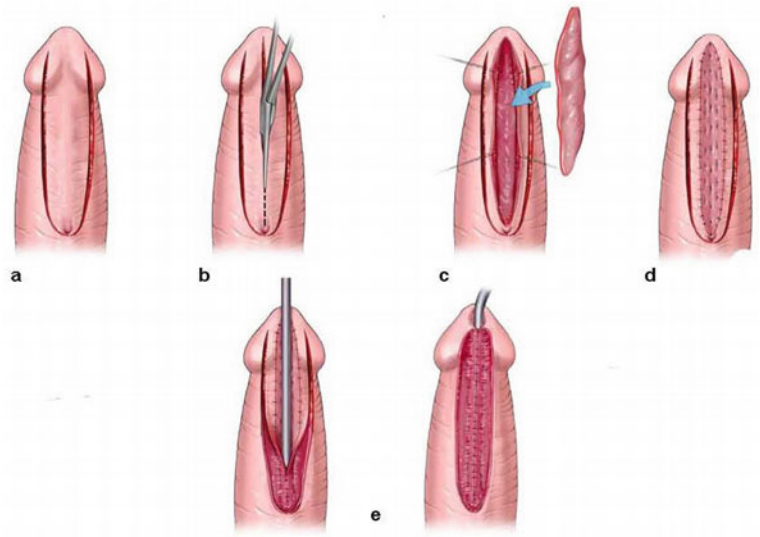

Fig. 9.7. Inlay graft. **a**: A strip of skin is outlined as a neourethral plate. **b**: A midline relaxing incision widens the skin strip. **c**: The midline defect is filled with a buccal graft. **d**: The graft is quilted into place to increase the likelihood for revascularization. **e**: The skin strip is tubularized.

Staged Buccal Grafts

When there is gross scarring of the urethral plate or ventral skin, extensive hair in the neourethra, BXO, or persistent ventral curvature, excision of all scarred tissues, creation of a proximal urethrostomy and staged buccal graft urethroplasty can be used to replace the entire neourethra (Fig. 9.8). After an interval of approximately 6 months, second-stage tubularization of the now-vascularized tissue completes the repair. Graft take is reliable despite

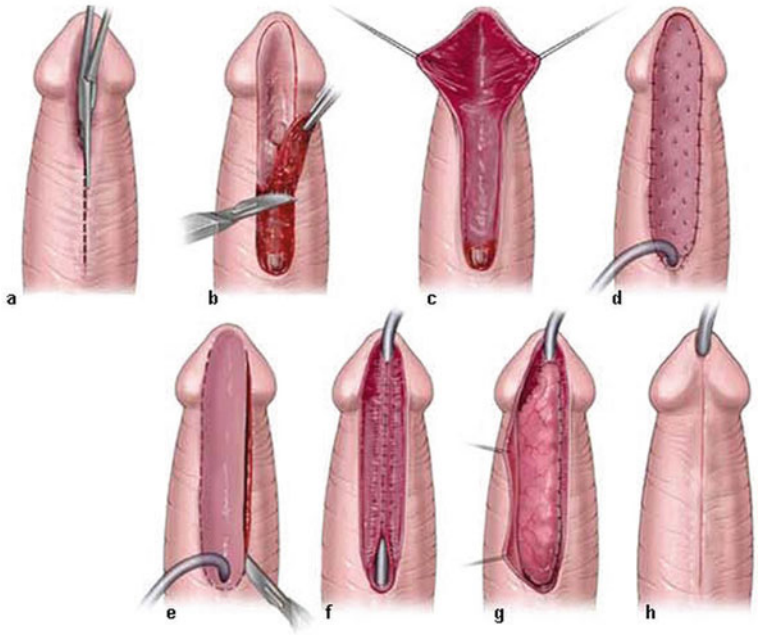

Fig. 9.8. Buccal Graft. **a**: Unhealthy neourethra is incised back to healthy urethra. **b**: Scarred tissues are excised along the ventral penile shaft. **c**: Midline fibrotic tissues are removed between glans wings creating a deep glanular groove. **d**: Buccal graft is quilted into place from the proximal urethrostomy to the tip of the glans. **e**: The second stage begins with a "U"-shaped incision. **f**: The buccal strip is tubularized in two layers; in-turning the epithelium. **g**: Dartos or tunica vaginalis flaps cover the neourethra. H: Glansplasty and skin closure is completed.

multiple failed operations, facilitated by quilting the buccal tissue directly to the tunica albuginea of the corpora cavernosa. Advantages of this approach are avoidance of skin flaps in cases when there often is a paucity of skin remaining, ability to directly observe the take of the graft between stages, and establishment of a deep glans groove to ensure a vertical, slit meatus. If contracture of the graft occurs either an inlay graft can be performed at the second stage, or if fibrosis precludes this the involved area can be excised and re-grafted in an interval step before creation of the neourethra. Staged buccal grafting simplifies repair of hypospadias cripples regardless of the number of prior operations and extent of penile scarring (*15*).

LONG-TERM RESULTS OF HYPOSPADIAS REPAIR

There is little long-term data available for any of the operations discussed above in common use today. Throughout the history of hypospadias repair continued evolution of techniques has often resulted in new operations being applied and then discarded before long-term results are determined.

Furthermore, most operations in the US are performed in the first year of life, and it is not reasonable to expect data to be available on more than a sampling of these patients after they complete puberty.

A single report (*16*) of teens and men operated during childhood mostly for midshaft to proximal hypospadias using tubularized prepucial flaps found most satisfied with the appearance and function of their penis, although nearly all had some spraying of their urinary stream, a weak stream, and/or terminal dribbling. In addition, half those experiencing ejaculation had to milk semen from the urethra. These outcomes are not surprising, given that skin tube neourethras inevitably are irregular and lack corpus spongiosum. Whether tubularized urethral plates covered by corpus spongiosum and without skin flaps will give different long-term results is not yet known.

REFERENCES

1. Kaefer, M., Diamond, D., Hendren, W. H. et al.: The incidence of intersexuality in children with cryptorchidism and hypospadias: stratification based on gonadal palpability and meatal position. J Urol, **162**: 1003, 1999
2. Snodgrass, W. T., Khavari, R.: Prior circumcision does not complicate repair of hypospadias with an intact prepuce. J Urol, **176**: 296, 2006
3. Luo, C. C., Lin, J. N., Chiu, C. H. et al.: Use of parenteral testosterone prior to hypospadias surgery. Pediatr Surg Int, **19**: 82, 2003
4. Timing of elective surgery on the genitalia of male children with particular reference to the risks, benefits, and psychological effects of surgery and anesthesia. American Academy of Pediatrics. Pediatrics, **97**: 590, 1996
5. Cote, C. J., Zaslavsky, A., Downes, J. J. et al.: Postoperative apnea in former preterm infants after inguinal herniorrhaphy. A combined analysis. Anesthesiology, **82**: 809, 1995
6. Cook, A., Khoury, A. E., Neville, C. et al.: A multicenter evaluation of technical preferences for primary hypospadias repair. J Urol, **174**: 2354, 2005
7. Snodgrass, W. T., Koyle, M. A., Baskin, L. S. et al.: Foreskin preservation in penile surgery. J Urol, **176**: 711, 2006
8. Nguyen, M. T., Snodgrass, W. T.: Effect of urethral plate characteristics on tubularized incised plate urethroplasty. J Urol, **171**: 1260, 2004
9. Baskin, L. S., Duckett, J. W., Ueoka, K. et al.: Changing concepts of hypospadias curvature lead to more onlay island flap procedures. J Urol, **151**: 191, 1994
10. Baskin, L. S., Erol, A., Li, Y. W. et al.: Anatomical studies of hypospadias. J Urol, **160**: 1108, 1998
11. Kajbafzadeh, A. M., Arshadi, H., Payabvash, S. et al.: Proximal hypospadias with severe chordee: single stage repair using corporeal tunica vaginalis free graft. J Urol, **178**: 1036, 2007
12. Bhat, A.: Extended urethral mobilization in incised plate urethroplasty for severe hypospadias: a variation in technique to improve chordee correction. J Urol, **178**: 1031, 2007
13. Nguyen, M. T., Snodgrass, W. T.: Tubularized incised plate hypospadias reoperation. J Urol, **171**: 2404, 2004
14. Schwentner, C., Gozzi, C., Lunacek, A. et al.: Interim outcome of the single stage dorsal inlay skin graft for complex hypospadias reoperations. J Urol, **175**: 1872, 2006
15. Snodgrass, W., Elmore, J.: Initial experience with staged buccal graft (Bracka) hypospadias reoperations. J Urol, **172**: 1720, 2004
16. Lam, P. N., Greenfield, S. P., Williot, P.: 2-stage repair in infancy for severe hypospadias with chordee: long-term results after puberty. J Urol, **174**: 1567, 2005

10 Varicoceles, Hernias, and Hydroceles

Ross Bauer and Barry A. Kogan

Abstract Varicoceles, hernias, and hydroceles are three common presenting complaints seen by urologists. Varicoceles are found in about 15% of the adolescent population. Varicoceles are easy to diagnose on physician examination by a primary care provider and are almost always asymptomatic. Treatment is needed only to improve fertility, which is not an issue for most teens. Further, semen analysis is difficult to obtain and of questionable utility in the adolescent population, hence treatment should be approached with caution. At this time, persistent volume discrepancy is the principle indication for surgical intervention. For most, routine annual or biennial physical examination for testicular volume should suffice. Pediatric hernias and hydroceles are also a common occurrence and are evaluated routinely in the urologist's office. The overall incidence of pediatric inguinal hernias ranges from 1 to 4%, with the incidence being 10× greater in males than females. Standard of care is open repair through an inguinal incision with high ligation of the hernia sac. Laparoscopic inspection of the contralateral internal ring through the patent processus vaginalis is a useful adjunct.

Keywords Hernia (direct and indirect) · Hydrocele (communicating and noncommunicating) · Varicocele · Pediatric · Adolescent · Infertility · Processus vaginalis · Laparoscopy

VARICOCELE

Introduction

Varicoceles are the most correctable cause of male infertility. They are present in 15% of the normal population and in 40% of men with infertility (*1*). Varicoceles are an abnormal dilation of the pampiniform venous plexus and internal spermatic vein and are often classified as clinical or subclinical. They are predominantly left sided, are rarely observed before puberty,

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and in certain cases are associated with ipsilateral testicular loss. There is a strikingly high incidence in early-mid teens, with ranges from 19 to 26% being reported and again 90% of the time they are on the left side (*2*). Since the incidence is high and varicoceles are easy to diagnose on physical examination by a primary care provider, the urologist must be prepared to deal with a large number of asymptomatic teens with this condition.

Detection of Varicoceles

All patients should have a complete history and physical at their initial evaluation. Varicoceles are almost always asymptomatic. Some boys may state that they have felt a painless sac adjacent to their testicle. Many will be diagnosed by their primary care physician and most will probably not be diagnosed as many primary care physicians fail to examine their patients in the upright position. Rare patients complain of "discomfort," some of which may be related to a feeling of being different. The physical exam should be done in both the supine and upright position (*1*). If there is trouble palpating a suspected varicocele, the patient may be asked to perform a valsalva maneuver to help in palpation. Most often the varicocele is an incidental finding found by the physician on physical exam in the upright position, classically being described as "a bag of worms" (*2*). Most varicoceles should decompress when the boy is supine and hence may be missed on examination only in the supine position. The rare varicocele that remains large in the supine position is suspicious for an obstruction of the left renal vein and the left kidney and retroperitoneum should be imaged, generally with ultrasound. This is also appropriate if the boy has hematuria in addition to a varicocele.

Varicoceles are graded based on physical exam findings as follows:

- Grade 1: Palpable only during valsalva maneuver
- Grade 2: Palpable without any maneuver
- Grade 3: Visible to the examiner's eye (*2*)

The measurement of testicular volume is an important part of the physical exam in order to help assess whether there are any testicular effects of the varicocele. Several methods are available to measure the size of the testis, including visual comparison, calipers, Prader orchidometer (comparative ovoids), Takahira orchidometer (disk elliptical rings), and ultrasound. Measurement of testis volume is assessed accurately and reproducibly by using either a Prader or disk orchidometer, or ultrasound (*3*). Ultrasound has been thought to be the most reliable. In clinical studies comparing Prader orchidometer and ultrasound in adolescents with a varicocele, 24% of patients with growth arrest would have been missed and 14% would have been identified falsely to have a significant size discrepancy if measured by Prader orchidometer alone (*3*). Ultrasonographic findings are considered positive if there is the presence of multiple veins >3.0–3.5 mm

with concomitant reversal of flow after Valsalva (*4*). Unfortunately, during puberty there are limited data on normal testicular growth and no evidence that both testicles develop at the same rate over the same time. Hence in teens, the diagnosis of a testicular effect of the varicocele is particularly problematic. Given this, the pediatric urological community has come of with guidelines, albeit, somewhat arbitrary ones. In general, if the affected testicle has a volume discrepancy of 2 ml or greater, or if there is a >20% difference between the contralateral and affected testicle this is considered significant. Without long-term follow-up it is difficult to determine whether the size difference is due to failure to grow during puberty or whether it is due to loss of volume, hence the term generally used is hypotrophy (*5*). In our practice, we use the Prader Orchidometer to assess for testicular volume in-office. The orchidometer is an easy and quick way to assess for testicular volume initially and provides a simple way to assess changes to testicular size over time. Ultrasound may be somewhat more accurate quantitatively, but is vastly more expensive. Although controversial, we feel that significant changes in testicular size can be found with the Prader orchidometer. If a difference in size is not appreciated on physical examination and can only be determined by ultrasound, we do not feel it is likely to be clinically relevant.

Subclinical varicoceles have also received attention in the literature. Subclinical varicoceles are not identifiable on physical exam and can only be seen on ultrasound. A subclinical varicocele is an abnormality of testicular blood flow characterized by measurable venous reflux without a clinically detectable varicocele (*6*). Subclinical varicoceles have, in adults, been associated with stress parameters on semen analysis. As in clinical varicoceles, subclinical varicoceles may also be associated with decreased testicular volume. Cervellione and associates found that 17% of normal boys screened had subclinical varicoceles and that 28% progressed later to clinical varicoceles, although their high index of suspicion may have altered the results. They advocate that children with subclinical varicoceles are in need of long-term follow-up (*6*). If one truly believes this theory, all boys would need to be screened with ultrasound for subclinical varicoceles. At this time in our practice we do not routinely check boys for subclinical varicoceles and we are not convinced that there is any value in this. Further prospective studies will help elucidate the need for testing and follow-up.

Risk Factors

Which adolescents are at risk for varicocele formation? There are numerous theories present in the literature. The predominance of left-sided varicoceles and the unique anatomy of left testicular vein are the basis for several theories explaining the cause of the disease. The “nutcracker effect” is thought to occur when the left renal vein is compressed between the

superior mesenteric artery and aorta, proximal to the point where the left testicular vein inserts. The subsequent increase of the hydrostatic pressure could result in varicocele formation. Other theories include increased arterial blood flow to the testis at puberty exceeding the venous capacity and/or elevated levels of nitric oxide in the plexus pampiniformis. A more likely cause for the development of a varicocele in the adolescent is an incompetent venous valve system. If the former explanations are true, it is hard to explain why ligating the veins completely in the retroperitoneum is an effective treatment, yet this fits well with the latter explanation.

There seems to be a genetic susceptibility, considering that 50% of first-degree relatives and 70% of brothers of men with varicocele also had a palpable varicocele. In a study from Bulgaria, increased height, penile length, and penile circumference were associated with increased risk of varicocele, whereas increased BMI had a protective effect (*7*). We have also found that tall, thin boys are more prone to a varicocele (although it has been argued that varicoceles may simply be harder to diagnose in obese boys) (*8*).

Classic teaching states that 45% of infertility is due to male factors. Varicoceles are the number one correctable cause of male infertility and many estimate that 40–50% of male factor infertility is due to varicoceles. In adults, semen samples from infertile men with varicoceles have shown decreased motility in 90% of patients. Sperm concentrations of less than 20 million sperm per milliliter were also found in 65% of the patients. Abnormalities in sperm morphology, including increased numbers of amorphous cells and immature germ cells, have also been found in infertile men with a varicocele (*9*).

Multiple theories are present to explain the mechanism for how a varicocele is able to disrupt normal testicular function. Despite extensive research, the exact cause of infertility in men having a varicocele is still not known. Alterations in temperature, hemodynamics, reactive oxidative species, and antioxidant concentrations have all been demonstrated to produce deleterious effects on spermatogenesis. Any one or all of these factors may play a role in infertility (*10*). The most likely explanation is that the venous congestion leads to higher testicular temperatures. For teens in particular, the pathophysiology is likely to extend over many years. In current medical practice, impairment of semen parameters, particularly sperm count, motility, and morphology, suggest that a varicocele might be clinically relevant (*11*). Unfortunately, obtaining a semen analysis is not generally feasible in teens, especially early teens. Interest has focused on adolescents with varicoceles because of the significant improvement of the sperm concentration and motility seen in adults after varicocele treatment in the face of infertility. The basic, as yet unanswered question is, “can early varicocelectomy be preventive?” Indeed, varicocelectomy in the adolescent population has been proposed as a therapeutic intervention both to preserve fertility and to preserve testicular growth (*7*). For obvious reasons, data confirming that this intervention is beneficial are limited.

Adolescents and Varicoceles

Idiopathic varicocele is one of the most common andrologic diseases in hypofertile males, influencing male reproductive capacity by affecting semen quality and quantity. Many studies have described the relationship between varicocele and hypofertility/infertility. In adults, varicoceles are identified often during the workup for infertility and semen samples are obtained. Varicocelectomy has been shown to increase motility, morphology, and sperm concentration in both the adolescent and adult population (*5*, *11*). In adolescents, sonographically derived volume differentials greater than 10–20% between normal and affected testes has been shown to correlate with a significantly decreased sperm concentration and total motile sperm count (*5*, *12*). Unfortunately in the pediatric age group, most varicoceles are detected incidentally and in teenagers it is often not possible to perform a preoperative semen analysis. Also, there are limited data to determine normal semen parameters in the pediatric population (*2*). For this reason, there are no references or predictive values for comparison with the pre- or post-operative semen analysis to determine whether there is any functional improvement related to the varicocelectomy. Very often, an empirical approach is used to decide how to treat varicocele because its early treatment may prevent hypofertility/infertility.

Varicocelectomy is performed if the homolateral testis develops hypotrophy or if pain is present (*13*). Zampieri et al. reported that testicular hypotrophy is the most objective indicator for surgical repair (*14*). In adolescents with ipsilateral testicular hypotrophy, it has also been shown that catch-up growth can be readily achieved in 50–80% of adolescents after varicocelectomy (*15*–*18*). Whether varicocelectomy is truly preventive of future infertility remains to be elucidated. Certainly, caution should be used in choosing surgery in these patients as there are no randomized long-term studies demonstrating a benefit.

Conclusion

Varicoceles are found in at least 15% of the adolescent population and are a frequent issue for the urologist. As they are asymptomatic and because semen analysis is difficult to obtain and of questionable utility, treatment should be approached with caution. At this time, persistent volume discrepancy is the principal indication for surgical intervention. For most, routine annual or biennial physical examination for testicular volume should suffice. Semen analysis can be offered in older teens though it is not fully clear that the results should be used as an indication for surgery.

HERNIA

Introduction

Pediatric hernias are a common occurrence and are evaluated routinely in the pediatric urologist's office. The vast majority of pediatric hernias are

inguinal, and the majority of these hernias are indirect. The overall incidence of pediatric inguinal hernias ranges from 1 to 4%, with the incidence being 10× greater in males than females (*19*).

The genetics of inguinal hernias are also poorly understood but there seems to be a genetic risk for siblings of patients with inguinal hernias. In general, the risk for brothers of a sibling is around 4–5 times the risk for a sister of an affected brother (*20*). Multiple genetic theories have been suggested, but no definitive connection has been validated.

Pathophysiology

Indirect inguinal hernias in children are an arrest of embryologic development rather than an acquired weakness. The formation of inguinal hernias in children is directly linked to descent of the developing gonads. The descent of the testes from the embryologic retroperitoneum begins early in gestation. As the mesonephros ascends into its usual position in the retroperitoneum, the testes remain at the level of the internal ring (*21*). During the third month of gestation the peritoneal lining of the abdominal cavity, which is the processus vaginalis, protrudes out of the internal ring following the gubernaculum. The gubernaculum attaches to the base of the scrotum in males and the labia majora in females (*22*). During weeks 28–36, the final descent of the testes into the scrotum occurs. In normal development, the processus vaginalis closes after testicular descent, obliterating the peritoneal opening of the internal ring between the 36th and 40th week of gestation. This portion of the processus vaginalis obliterates, except for the part that becomes the tunica vaginalis. If the processus fails to obliterate, there is an opening between the peritoneal cavity and the scrotum, providing a channel for fluid, bowel, and omentum to pass (*22*). If the opening in the processus vaginalis is small, a hydrocele will develop (refer to section on hydrocele for further discussion). If the opening is large enough, bowel or omentum may pass, resulting in a hernia.

There is some confusion regarding the nomenclature of inguinal hernias in the pediatric population, as some believe that a patent processus vaginalis is the same as an inguinal hernia. Although a patent processus vaginalis is required for hernia formation, the presence of a patent processus vaginalis does not always mean a hernia is present. The classic teaching has been that approximately 20% of boys have a patent processus vaginalis at 2 years of age (*21*). It is assumed that closure will continue during childhood for some patients, but there are no firm data to support this. Certainly, some of these 20% will develop clinically significant symptoms and will require operative intervention. In a 2007 study from the Netherlands, over 300 adults undergoing unilateral hernia repair were followed. During surgery all had laparoscopic exploration of the contralateral internal ring. In 12% of these patients there was a patent processus vaginalis. These patients were then followed for an average of 5.5 years and inguinal hernias developed in 12%

of adult patients with a patent processus vaginalis. This is a rate four times greater than in the adults in the study who had a closed ring (*23*). This study suggests that, in adults, a patent processus vaginalis has significant risk of developing a hernia. One would guess that this risk would be increased in children who may live 80 years after the discovery of a patent processus, but that data are not available.

Diagnosis

Diagnosing an inguinal hernia may be difficult in the pediatric population. Most often the child presents with a "bulge" or the parents states that a bulge is present with activities that increase intra-abdominal pressure, i.e. coughing, laughing. The bulge disappears when intra-abdominal pressure returns to normal. In older children the hernia may be apparent during the day and disappear at night. Sometimes the lesion is only reported by the parent but is not seen or felt during examination. There are many ways to elicit an increase in pressure to identify the hernia. For children that are old enough, asking them to cough is a quick and easy way. For children too small to cough on command or those that do not follow directions, other methods can be used to increase intra-abdominal pressure. For babies, holding their legs and arms gently against the examination table so they cannot move usually elicits a crying response. For slightly older children tickling them to make them laugh or having them blow up balloons (i.e., examination gloves) will increase intra-abdominal pressure (*24*). Sometimes the physician can elicit the "silk glove sign." This name refers to the feeling of silk rubbing against silk and describes the movement of the layers of the processus vaginalis around the spermatic cord. The accuracy of the "silk glove sign" is highly variable and dependent on the observer. In some cases it is felt to be very good. Most recently a study from Taiwan prospectively reviewed their experience of 1,040 pediatric patients with inguinal hernias. A total of 180 (19.8%), of whom 154 were boys and 26 were girls, had a positive silk glove sign. Their sensitivity for detection of hernia was 93.1% and the specificity was 97.3% (*25*). In our experience, this is likely to be an overestimate of its usefulness. At this time in our practice we use the silk glove sign as a complement to hernia evaluation but would not recommend surgical intervention based on it alone. In some instances determination of the presence of a hernia is based solely on the history given by the parents. In our practice we do repair hernias based on parents who are good historians, although visualized evidence is always preferred. We encourage parents to obtain a digital photograph of the pathology when we are unable to document anything in the office. Herniography has also been touted as a tool to help diagnose abdominal hernias. A 60% iothalamate solution is injected into the peritoneum with a small needle. The child is then placed in the upright position and an X-ray is taken after 10 min. The solution then outlines the patent processus vaginalis if present (*22*). It has been shown to

have high rates of sensitivity and specificity (*26*) but the risk of bowel injury, contrast reactions, and peritoneal irritation make this a seldom-used modality in 2010 (*22*). Finally, scrotal ultrasound has been described as a tool to evaluate inguinal hernias. It has been reported that a hypoechoic structure 4–6 mm in diameter in the inguinal canal is a patent processus vaginalis where >6 mm is an inguinal hernia (*27*). Currently we are not routinely using pre-operative ultrasound in our workup of pediatric hernias.

If a hernia is found by examination (by definition with bowel in it), attempts should be made to reduce the hernia. This can usually be performed by providing gentle pressure on the hernia. It is important that the child be relaxed during this maneuver, as high intra-abdominal pressure will work against reducing the hernia. In cases where there is a fear of incarcerated bowel (tender mass, erythema on the skin), attempts should be made to reduce the hernia. If it cannot be reduced, the patient should be brought to the operating room for emergent operative intervention. Not only is the bowel at risk, but the blood supply to the testis is likely to have been cut off and there is a high risk of testicular damage. If the hernia is able to be reduced, observation of the patient is important to ensure that no bowel injury has occurred. Even when there is no evidence of a bowel injury, the patient should be scheduled for operative repair soon after.

Treatment

The main reason for doing elective hernia repair in children is the fear of incarceration with the need for acute operation, with the potential for bowel or testicular injury. The exact risk of incarceration is, however, not known as there are no observational studies in the literature where children with known hernia have been observed without planned elective surgery. Operative series have reported rates of incarceration of approximately 30% in newborns, decreasing to 10–15% at 1 year, and further down to 1% at 8 years. Preterm babies seem to have a special high risk of incarceration (*28*).

The gold standard for surgical repair is an open repair performed by ligating the processus vaginalis at the internal ring. Success rates for the operation approach 99%. The major risk from the surgery is from the anesthetic, although there is also a 1% risk of damage to the spermatic cord during elective hernia repairs. This risk increases to 6–10% when operating on an incarcerated hernias, hence the recommendation for elective repair (*22*). Other reported complications include a risk of wound infection in 1.2%, testicular atrophy in 1–2%, and decreased testicular size in 2.7–13% of patients (*29*). Iatrogenic cryptorchidism occurs in 0.6–2.9% of patients and injury to the vas deferens is reported to be 0.13–0.53%. Although extremely rare, infertility as a result of injury to the fallopian tubes has been reported in girls (*29*). Most believe that a mesh repair in children should not be performed as there is a significant chance for inflammatory reaction, which has been reported to cause obstruction of the vas deferens.

Whether there is a need for contralateral exploration when performing a unilateral inguinal hernia repair is a question somewhat unique to children. In 75–90% of patients the hernia is unilateral at the time of presentation but after surgical repair some children develop a hernia on the opposite side (*30*). If a child develops a second hernia, this almost always requires a second operation. As stated earlier, there is a high risk of metachronous contralateral hernia in children with a unilateral inguinal hernia who have a contralateral patent processus vaginalis. Some argue that a hernia can be prevented by exploring the asymptomatic contralateral groin and closing any patent processus vaginalis. In the past, this has been advocated in all children under two. However, additional surgery is not without risk and some children would have unnecessary operations with potential injury to the vas or vessels. Recently, a systematic review of 49 papers and 22,846 patients found that 14 contralateral explorations are required to prevent one metachronous inguinal hernia. The risk of developing a contralateral hernia appears unchanged in early childhood, with a slight reduction after 12 years of age. Indeed, most contralateral hernias occur in the first 5 years after unilateral inguinal hernia repair (*30*). Children with a left-sided hernia have the greatest risk of developing a contralateral hernia, but even in this group, ten explorations are thought to be required to prevent one contralateral hernia. With the advent of laparoscopy, it has become easier to view the contralateral inguinal ring and assess for patency. Currently, both unilateral repair with observation or laparoscopic exploration with repair of a patent processus vaginalis are considered the standard of care with the exception of infants. At this time in our practice we do use laparoscopy to view the contralateral inguinal ring and recommend to the family that we fix the contralateral side if there is a patent processus vaginalis.

Conclusion

Hernias are a common problem seen in pediatric urology, with the most common being an indirect inguinal hernia. Standard of care is open repair with high ligation of the hernia sac. Contralateral exploration should be performed in infants and in older children, and either observation or laparoscopic evaluation of the contralateral internal ring is acceptable in older children. If there is a contralateral patent processus vaginalis, repair is indicated.

HYDROCELE

Background and Treatment

As discussed in the hernia section, the same patent processus vaginalis that causes a hernia is responsible for most cases of hydrocele formation in children. In the case of a hydrocele, the patent processus is smaller, allowing fluid to pass from the peritoneal cavity into the scrotum, but small enough

that bowel does not pass. Most hydroceles in infants and children result from persistence or delayed closure of the processus vaginalis. These are termed communicating hydroceles as there is a communication with the peritoneum. Most of these hydroceles resolve with spontaneous closure of the processus vaginalis during the first year of life. For those that do not resolve, it is thought that the persistent patent processus will eventually enlarge as the child grows and is more active and experiences higher intra-abdominal pressures. Hence elective repair is recommended. The history and physical examination in these cases is very characteristic. On history, it will be found that the size of the scrotum varies. In particular, it is usually small in the morning, enlarges with activity, and gets smaller again when the child sleeps. This is due to the peritoneal fluid being pushed into the scrotum with intra-abdominal pressure and the fluid returning when intra-abdominal pressure is lower. Similarly, on physical examination, the fluid, which transilluminates, can be pushed back into the peritoneum with gentle pressure (provided the child is not crying).

If the communicating hydrocele persists past a year of age (some might say 2 years of age), elective repair is recommended. For the adult urologist it is critical to note that the etiology of these hydroceles is the patent processus. They should never be approached through the scrotum like an adult hydrocele. The repair is identical to that of an inguinal hernia. We recommend a laparoscopic evaluation of the contralateral internal ring through the patent processus, as described above for an inguinal hernia repair.

A non-communicating hydrocele is an accumulation of fluid within the tunica vaginalis. These hydroceles are much more common in adults, but can occur in newborns when the fluid becomes trapped in the scrotum after obliteration of the processus vaginalis or when the fluid entering through the internal ring becomes loculated. These are seen in infants, transilluminate, can be large and tense, but are not painful. In general, those that are tense and difficult to reduce are most likely to have a small communication and therefore are best managed by observation. Most of these simple, tense scrotal hydroceles found at birth will resolve during the first 2 years of life. The testis should be either palpated or evaluated by transillumination or even ultrasound as an abnormal testis may also cause a non-communicating hydrocele. There is no role for aspiration of the fluid as this only serves as a nidus for infection in the scrotum, and if the processus is not fully obliterated, into the peritoneal cavity. A recent study looking at hydroceles not noticed until after 1 year of age also noted the benefit of at least 1 year of observation as 75% resolved spontaneously (*31*).

In children and adolescents, non-communicating hydroceles most often form secondary to inflammation of the epididymus or testis. The fluid comes from the mesothelial lining of the tunica vaginalis (*22*). The primary problem should be addressed. Some non-communicating hydroceles are not related to any testicular problem and are found as an incidental finding on physical

examination. When small, they should be ignored. Some will enlarge over time and if the hydrocele is causing distress, it should be repaired as in adults.

Special Consideration

Children who have increased intraabdominal pressure, e.g., those who are on peritoneal dialysis or those children with ventriculo-peritoneal shunts, are unlikely to have spontaneous closure of their defect and should undergo elective repair. These children also have a higher risk of recurrence after repair. Indeed, this is the one group for which we do not recommend a solitary suture ligature of the processus vaginalis. We have observed peritoneal fluid seeping from the suture site and recommend a free ligature tied above the suture ligature.

Conclusion

Hydroceles are a common problem seen by the urologist. Many resolve with time. For those that do not resolve, surgical management via an inguinal approach is the treatment of choice.

REFERENCES

1. *Report on varicocele and infertility*. 2001, American Urological Association (AUA) & American Society for Reproductive Medicine (ASRM)
2. DiSandro, M., *Adolescent urology: testicular torsion, varicoceles, and gynecological problems*, in *Handbook of Pediatric Urology*, L. Baskin, B. Kogan, Editor. 2005, Lippincott Williams & Wilkins: Philadelphia. pp. 179–181.
3. Bong, G.W. and H.P. Koo, *The adolescent varicocele: to treat or not to treat*. Urol Clin North Am, 2004. **31**(3): 509–15, ix.
4. Lee, J., et al., *Varicoceles: The Diagnostic Dilemma*. 2007. jandrol.107.003467.
5. Cayan, S. and C.R. Woodhouse, *The treatment of adolescents presenting with a varicocele*. BJU Int, 2007. **100**(4): 744–7.
6. Cervellione, R.M., M. Corroppolo, and A. Bianchi, *Subclinical varicocele in the pediatric age group*. J Urol, 2008. **179**(2): 717–9.; discussion 719.
7. Kumanov, P., R.N. Robeva, and A. Tomova, *Adolescent varicocele: who is at risk?* Pediatrics, 2008. **121**(1): e53–57.
8. Delaney, D.P., et al., *The physical characteristics of young males with varicocele*. BJU Int, 2004. **94**(4): 624–6.
9. MacLeod, J., *Seminal cytology in the presence of varicocele*. Fertil Steril, 1965. **16**(6): 735–57.
10. Schoor, R.A., S.M. Elhanbly, and C. Niederberger, *The pathophysiology of varicocele-associated male infertility*. Curr Urol Rep, 2001. **2**(6): 432–6.
11. Agarwal, A., et al., *Efficacy of varicocelectomy in improving semen parameters: new meta-analytical approach*. Urology, 2007. **70**(3): 532–8.
12. Diamond, D.A., et al., *Relationship of varicocele grade and testicular hypotrophy to semen parameters in adolescents*. J Urol, 2007. **178**(4 Pt 2): 1584–8.
13. Schiff, J., et al., *Managing varicoceles in children: results with microsurgical varicocelectomy*. BJU Int, 2005. **95**(3): 399–402.
14. Zampieri, N., et al., *Longitudinal study of semen quality in adolescents with varicocele: to treat or not?* Urology, 2007. **70**(5): 989–93.

15. Gershbein, A.B., M. Horowitz, and K.I. Glassberg, *The adolescent varicocele I: left testicular hypertrophy following varicocelectomy*. J Urol, 1999. **162**(4): 1447–9.
16. Kass, E.J. and A.B. Belman, *Reversal of testicular growth failure by varicocele ligation*. J Urol, 1987. **137**(3): 475–6.
17. Stern, R., W. Kistler, and A.F. Scharli, *The Palomo procedure in the treatment of boys with varicocele: a retrospective study of testicular growth and fertility*. Pediatr Surg Int, 1998. **14**(1–2): 74–8.
18. Paduch, D.A. and J. Niedzielski, *Repair versus observation in adolescent varicocele: a prospective study*. J Urol, 1997. **158**(3 Pt 2): 1128–32.
19. Manoharan, S., et al., *Evidence-based change of practice in the management of unilateral inguinal hernia*. J Pediatr Surg, 2005. **40**(7): 1163–6.
20. Jones, M.E., et al., *Risk of congenital inguinal hernia in siblings: a record linkage study*. Paediatr Perinat Epidemiol, 1998. **12**(3): 288–96.
21. Brandt, M.L., *Pediatric hernias*. Surg Clin North Am, 2008. **88**(1): 27–43.
22. Kogan, B.A., *Hydrocele, Hernia, Neonatal Torsion, and Scrotal Masses*, in *Handbook of Pediatric Urology* L. Baskin, B. Kogan, Editor. 2005, Lippincott Williams & Wilkins: Philadelphia. pp. 51–57.
23. van Veen, R.N., et al., *Patent processus vaginalis in the adult as a risk factor for the occurrence of indirect inguinal hernia*. Surg Endosc, 2007. **21**(2): 202–5.
24. Lloyd, D., *Inguinal and femoral hernia*, in *Operative Pediatric Surgery*, A.R. Ziegler M., and Weber T., Editors. 2003, McGraw-Hill: New York. pp. 543–554.
25. Luo, C.C. and H.C. Chao, *Prevention of unnecessary contralateral exploration using the silk glove sign (SGS) in pediatric patients with unilateral inguinal hernia*. Eur J Pediatr, 2007. **166**(7): 667–9.
26. Garner, J.P., et al., *Is herniography useful?* Hernia, 2006. **10**(1): 66–9.
27. Erez, I., et al., *Preoperative ultrasound and intraoperative findings of inguinal hernias in children: A prospective study of 642 children*. J Pediatr Surg, 2002. **37**(6): 865–8.
28. Rosenberg, J., *Pediatric inguinal hernia repair-a critical appraisal*. Hernia, 2008. **12**(2): 113–5.
29. Tackett, L.D., et al., *Incidence of contralateral inguinal hernia: a prospective analysis.* J Pediatr Surg, 1999. **34**(5): 684–7; discussion 687–8.
30. Ron, O., S. Eaton, and A. Pierro, *Systematic review of the risk of developing a metachronous contralateral inguinal hernia in children*. Br J Surg, 2007. **94**(7): 804–11.
31. Christensen, T., et al., *New onset of hydroceles in boys over 1 year of age*. Int J Urol, 2006. **13**(11): 425–7.

11 Testicles: Undescended, Retractile, and Ascended

Katherine Moore and Antoine E. Khoury

Abstract The undescended testis in the newborn male is a frequent reason for urological consultation. Spontaneous descent after birth usually happens in the first 3 months of life and is essentially inexistent after 1 year of age. Infertility, malignant transformation, testicular torsion, and hernia are the main consequences associated with cryptorchidism. Surgery should be planned before the child's first birthday to decrease the risks of histological changes and to prevent further complications. A proper examination in the office by an experienced clinician establishes the diagnosis. A hormonal evaluation is mandatory if bilateral nonpalpable gonads are encountered. The surgical approach is planned according to the findings of the examination under general anaesthesia at the time of the repair. Preoperative radiological evaluation is not routinely necessary since it does not provide accurate information due to a high rate of false-positive and false-negative studies and does not eliminate the need for surgical exploration. Different surgical techniques may be used with high success rates. Nonetheless, basic principles in testicular mobilization and tissue handling should be respected to avoid complications.

Keywords Testicles · Cryptorchidism · Undescended · Retractile · Orchipodexy

INTRODUCTION

A nonpalpable or undescended testis in the pediatric population is a frequent reason for urological consultation. The goal of the treatment is to restore the normal position of the testicle in the scrotum in a timely fashion in order to optimize the potential for development and function. Despite the current recommendations for early correction or cryptorchidism, many of these children are still being referred late and are undergoing surgery beyond 12–18 months of age. This chapter will review the evaluation and the management of the patient with cryptorchidism.

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EMBRYOLOGY

The primordial germ cells are located in the caudal portion of the yolk sac during the 4th week of gestation. During the 5th and 6th weeks, they migrate along the dorsal mesentery of the hindgut toward the urogenital ridge. Sexual differentiation is initiated at 7 weeks of gestation and is controlled by the genes located on the sex-determining region on the short arm of the Y chromosome (SRY). During the 8th week, Sertoli cells start producing müllerian inhibiting substance (MIS) that triggers involution of the müllerian structures. Testosterone secretion by the Leydig cells begins around the 10th week. After birth, testosterone levels peak between the 30th and 90th days of life, decrease at 6 months, and then remain low until puberty. During this predominant androgenic period, the gonocytes will multiply and will transform into adult dark spermatogonia.

Testicular Descent

The testes remain in the upper abdomen until the 7th month of gestation, when they move from the abdominal cavity through the inguinal canals into both sides of the scrotum. It has been proposed that this migration occurs in two phases. The first phase, movement across the abdomen to the entrance of the inguinal canal, appears controlled (or at least greatly influenced) by MIS and descendin. The second phase, during which the testes move through the inguinal canal into the scrotum, is dependent on androgen production and on an increase of the intra-abdominal pressure.

ANATOMY

Histologically the testis is composed of two principal cell populations: Sertoli cells and Leydig cells. Each gonad is covered by several layers of tissues that constitute extensions of the abdominal wall layers (tunica albuginea, tunica vaginalis, internal spermatic fascia, cremasteric muscle and fascia, external spermatic fascia, dartos, and scrotal skin). The two testicles are separated in the scrotum by a longitudinal septum. The arterial blood supply comes from three different sources: the testicular artery arises from the aorta, the cremasteric artery from the inferior epigastric artery, and the vasal artery from the vesical artery. The venous return occurs through the pampiniform plexus that empties into the renal vein on the left side and directly into the vena cava on the right side. The lymphatic drainage of the gonad follows the vessels in their retroperitoneal course and is distinctly different from the scrotal skin drainage that is inguinal and more superficial.

DEFINITION

The term undescended testis describes a gonad that is abnormally positioned and located anywhere between the abdomen and the scrotum. This term has been used interchangeably with cryptorchidism. However, the term

cryptorchidism should only be used to describe a nonpalpable gonad if we strictly refer to the Greek roots *crypto* (hidden) and *orchid* (testicle). The undescended testicle may also be in an ectopic position. The gonad usually becomes ectopic when it fails to reach the scrotum after its descent through the external inguinal ring. The ectopic gonad may be femoral, perineal, suprapenile, in the controlateral hemiscrotum, or found in the Denis-Browne pouch between Scarpa's fascia and the external oblique fascia. An empty scrotum may also be a sign for an atrophic testis (nubbin), a vanished testis with blind-ending vessels, a true testicular agenesis or a retractile testicle, a gonad that withdraws in the inguinal canal secondary to an overactive cremasteric reflex but that can be easily repositioned back into the scrotum.

Overall, 20% of undescended testes are nonpalpable in the office. Of those, 18% will be palpated under anaesthesia (*1*). Therefore, the remaining gonads can be described as intra-abdominal, atrophic, or vanished.

EPIDEMIOLOGY

Unilateral undescended testicles are one of the most common congenital anomalies described at birth and are present in 3% of full-term newborn males (*2*). Bilateral cryptorchidism is less common than unilateral cryptorchidism and occurs in 1.6–1.9% of males. The prevalence of undescended testicles is higher in premature infants of 36 weeks or less, being estimated at 30% (*3*). This finding suggests that although the descent of the gonad in the scrotum is usually completed at the end of the second trimester, it may not be fully completed until close to term. The prevalence of cryptorchidism also declines from 3% at birth to 1% at 3 months of life and this percentage remains stable by 1 year of age and throughout adulthood. Between birth and 3 months of age, 70–77% of testes will descend spontaneously. Only 7% of cryptorchid gonads will reach their normal position in the scrotum beyond 6 months of age (*4*). Cryptorchidism occurs twice more frequently on the right side compared to the left side. A familial history of cryptorchidism and the weight at birth independent of the gestational age are the two most important determinants of cryptorchidism at birth and at 1 year of age (*5*).

CONSEQUENCES OF UNDESCENDED TESTICLES

Infertility

The extra-scrotal position of the gonad impairs germ cell development. The severity of the defects increases in correlation with the location of the testicle in the abdomen, and is worst for the high intra-abdominal gonads. However, all newborns with intra-abdominal gonads have normal counts of germ cells. The changes related to the cryptorchidism only become obvious between 1 and 2 years of age. They include a decreased number of Leydig cells, degeneration of Sertoli cells, delayed disappearance

of gonocytes, slow appearance of adult dark spermatogonia, failure of development of primary spermatocytes, decreased number of germ cells count, and peritubular fibrosis. The earliest change in the undescended testes is the hypoplasia of the Leydig cells that occurs in the first months of life. Similar anomalies have been found in the controlateral gonad. No relevant hormonal marker has been identified for the measurement of testicular function in prepubertal boys with cryptorchidism. Cortes et al. have measured the percentage of germ cell aplasia on biopsies done during orchidopexies and they have correlated their results with the age at surgery. In the general population, the incidence of germ cell aplasia is around 1% and this measure remains stable over time until puberty. However, biopsies of untreated cryptorchidism often show significant increase of aplasia starting at 15 months of age. Specifically, 20% of 2-year-olds, 40% of 6-year-olds and 45% of 10-year-olds will demonstrate a significant amount of germ cell aplasia (*6*). Those numbers suggest potential benefits for early treatment. Males with a previous history of undescended testes will have worse spermogram parameters compared to normal individuals. However, the paternity rate of men with unilateral cryptorchidism is similar to the general population and does not correlate with the age of correction or to the findings on a biopsy made at the time of the orchidopexy. Monorchidism secondary to absent, atrophic, or surgically removed testes does not appear to decrease the paternity rate. Among untreated men with bilateral cryptorchid testicles, none have normal fertility parameters but a quarter of those treated reach normal fertility rates (*7*). The paternity rate in the bilateral undescended testes population is evaluated to be around 50%. Experimental studies have demonstrated that orchidopexy at an early age can decrease and also reverse the histological anomalies in cryptorchidism, supporting the need for early recognition and treatment (*8*). Epididymal and vasal anomalies associated with the undescended testes can also explain the infertility in some patients with cryptorchidism and are recognized in 15–85% of patients at the time of surgery. The complications associated with the surgical treatment for the undescended testis should also be considered as potential causes of infertility. Iatrogenic trauma to the vas deferens is often unrecognized. Testicular atrophy can also occur following an orchidopexy as a result of compromise of the blood supply. Deep intraparenchymal sutures can also induce an inflammatory reaction in the testis with resultant parenchymal injury.

Neoplasia

Males born with undescended testicles are at higher risk of developing testicular malignancy and will usually develop it after puberty. Ten percent of all testicular cancers arise from cryptorchid testicles (*9*). The initial location of the testis correlates with the relative risk of neoplasia: the higher the testicle is in the abdomen, the higher the risk of malignant transformation.

The risk is six times higher for an abdominal gonad compared to an inguinal testicle. The most frequent cancer that arises from an undescended testis is a seminoma (*10*). The prevalence of carcinoma in situ is 1.7% in the cryptorchid organ (*11*). It is unclear whether malignant transformation develops as a result of an intrinsic abnormality of the testis or due to its nondescent. The orchidopexy, however, allows for easier self-examination and therefore, in theory, earlier detection of any testicular mass. However, no difference has been found between the surgically treated and untreated groups, the rate of metastatic disease at presentation and the cancer-specific survival rate being the same in the both groups (*12*). The main difference for testicular cancers in undescended testicles is the higher rate of positive inguinal lymph nodes if an orchidopexy was performed. Pettersson et al. reported on a large cohort of men in Sweden who underwent surgical treatment for undescended testicles and identified 56 testicular cancers among 16,983 men. The relative risk of malignancy was lower (2.23) in the group that was operated on before puberty compared to the group treated after 13 years of age (5.40) (*13*). This study confirmed that the treatment of undescended testes before puberty may decrease the risk of testicular cancer and supports the evidence published earlier by Moller et al. that the relative risk of testicular cancer in patients treated for cryptorchidism increases with the age at the time of treatment (*14*).

Testicular Torsion

The cryptorchid gonad has an increased risk of torsion when untreated compared to the normally descended testis. It has been hypothesized that this event is the result of an anatomic abnormality between the testicle and its mesentery during development. An extra-scrotal testicular torsion should be considered in a male suffering from abdominal or inguinal pain with an empty ipsilateral hemiscrotum. This event should prompt early and careful evaluation of the affected gonad since Riegel found that 64% of adults with torsion of an undescended testis have an associated germ cell tumour at the time of resection (*15*).

Hernia

A patent processus vaginalis is found in 90% of the cases of undescended testes (*16*). The processus vaginalis usually obliterates between the moment of the descent of the testicle and the first year of life. The patency of the processus vaginalis increases the risk of hernia and hydrocele development. Dissection of the hernia sac off the cord structures and high ligation of the sac at the internal ring are essential manoeuvres during orchidopexy that provide length to allow adequate positioning of the testis in the scrotum.

DIAGNOSIS

History and Physical Examination

Every evaluation of a male with cryptorchidism starts with a complete history and physical exam. The questionnaire should include the obstetrical and maternal history and should document the use of steroids. The medical, surgical, and family histories should also be included. Twenty-three percent of males with an undescended gonad will have a positive family history of cryptorchidism compared to 7.5% for control families (*17*). Finally, the age, the weight, and the scrotal examination at birth complete the questionnaire. A previous history of normal descended testes in the first year of life is usually difficult to obtain. However, an empty scrotum after a previously documented normal exam can reflect testicular ascent or a vascular event with atrophy. The ascent of the gonad can be iatrogenic after a hernia or a hydrocele repair. It can also be primary, due to progressive muscular spasticity (cerebral palsy) or by retraction of the processus vaginalis during its closure. Idiopathic testicular ascent will resolve at puberty in 57% of men without any significant testicular volume lost (*18*).

The physical exam requires a quiet and warm room and a relaxed child supine with his legs placed in a frog-like position. Inspection for birth defects and syndromic features should be part of the exam. Observation of the genitalia includes evaluation of the penis for anomalies such as hypospadias and ambiguous genitalia. The prevalence of simultaneous cryptorchidism and hypospadias is directly related to the position of the meatus: 30% of the patients with a proximal hypospadias will have an associated undescended gonad compared to 2.5% for the patients with a glandular hypospadias. Scrotal development, inguinal canals, and common sites of testicular ectopic gonads should also be inspected. For cases of unilateral undescended testis, the controlateral gonad should also be evaluated for its size and consistency. A hypertrophied gonad, usually defined as a volume of more than 2 ml will suggest the presence of a controlateral atrophic testis; however, it is not sufficient and reliable to confirm the diagnosis (*19*). Evaluation of the cremasteric reflex (under the control of the genitofemoral nerve), by palpation of the inner thigh, can allow identification and localization of the testicle. The cremasteric reflex is absent in the newborn. In children, its activity is inversely proportional to the levels of testosterone and is more active between 3 and 9 years of age. Palpation of the undescended testis should be performed with warm hands and lubricant on the fingertips. By sliding the lubricated finger tips from the anterior superior iliac spine over the inguinal canal toward the scrotum, a testicle at the internal ring or in the inguinal canal is usually felt as the tips of the fingers slide over it stretching the cord causing the testicle to snap back in position once the fingers pass it. A nonpalapable testis may be intra-abdominal or vanished/atrophic testis. A retractile testis typically retracts to the superficial inguinal pouch but can be milked into the scrotum at least 5 cm below the

pubic tubercle. A retractile testis should be followed yearly until puberty for its risk of ascent (*20*). The areas of common testicular ectopia should also be palpated to complete the physical evaluation.

Radiological Evaluation

The overall accuracy of radiological evaluation for the undescended testis is 44% (*21*). Imaging with ultrasound, computed tomography, and even magnetic resonance, which are all used to localize and to determine the presence of the cryptorchid gonad, is not superior to a physical examination when planning for surgery. Their rates of false-negative and of false-positive results are significant and should not influence the decision made following the physical examination. Cain et al. reported that testicles were identified by ultrasound in 70% of the cases when palpable and only in 15% if they were unpalpable. Overall, they reported 5% of false-positive and 40% of false-negative results (*22*). The rates of false-negative CT scan and MRI studies are 15 and 10%, respectively. Because the surgical exploration is mandatory, imaging for the undescended testis is an unnecessary expense. The use of radiological evaluation should be limited to cases of ambiguous genitalia to evaluate the presence of müllerian structures and for cases of true testicular agenesis or vasal agenesis that are associated with 20% incidence of ispilateral renal agenesis.

Hormonal Evaluation

A karyotype and hormonal evaluation should be performed for all cases of bilateral nonpalpable gonads and for cases of unilateral undescended testes when associated with hypospadias or ambiguous genitalia. This evaluation determines the presence of functional testicular tissue. The karyotype not only guides further investigation but is important in diagnosing life-threatening events such as salt-wasting congenital adrenal hyperplasia. Measurement of gonadotropin levels, principally the follicle-stimulating hormone (FSH), should also be obtained. An elevated level of FSH with a low testosterone level in a prepubescent child with normal male karyotype signifies bilateral anorchia. If the gonadotropin levels are normal, an hCG stimulation test can confirm the presence of functioning testicular tissue. The conventional regimen uses 1500 U/m^2 of hCG in six injections over a period of 3 weeks. FSH, LH and DHT are measured before the stimulation and 72 h following the last dose. A favourable response, which indicates the presence of testicular tissues, is defined by a three time increase of the baseline testosterone level. However, a false-negative result may be obtained if the Leydig cells are unresponsive to exogenous hCG. Therefore, all children with a normal karyotype, bilateral unpalpable testicles, normal gonadotropin levels and with or without a conclusive hCG stimulation test should undergo a surgical exploration to confirm the absence of intra-abdominal gonads since they may be present 15% of the time. MIS and inhibin B are other

markers of testicular function that can be measured. MIS is secreted by the Sertoli cells as early as the 8th week of gestation and until puberty. This is a specific marker for functional testicular tissues. The levels are undetectable in cases of bilateral anorchia or dysgenetic gonads. Low levels of MIS are inconclusive for absence of testicular tissues and surgical exploration is still required.

MANAGEMENT

Hormonal Treatment

The rationale behind the hormonal treatment for an undescended testis is based on experimental observations that showed that the testicular descent is mediated by testicular androgen synthesis. The potential advantages of the hormonal treatment are to prevent the need for surgery and to ameliorate the parameters of the spermogram, according to some authors (*23*). Polascik et al. reported an increase of the testicular vascularization and a simpler orchidopexy after hormonal therapy (*24*). Two products, for which different regimens have been described, can be used: hCG that directly stimulates Leydig cells to produce testosterone and GnRH that activates the hypothalamic-pituitary-gonadal axis. Successful results are more common in children with retractile testes or testicles below the external inguinal ring. The hormonal treatment is not indicated for patients with ectopic gonad, inguinal hernia or previous history of surgery. It is contraindicated in immunosuppressed patients because it induces a transient decrease of lymphocytes. Hormonal stimulation can also induce virilisation of the external genitalia with pigmentation of the scrotum, increase the size of the penis, and induce pubic hair growth and early closure of epiphyseal plates. HCG stimulation also induces some histological changes in the gonads described as an increase of the density of interstitial tissues and blood vessels. However, hCG withdrawal seems associated with increased apoptosis of germ cells. Overall, the success rate of hormonal treatment is less than 20% and is highly dependant on the testicular location (*25*). Long-term follow-up should be planned after successful treatment because re-ascent in as much as 25% of the cases has been reported. As a result of the poor and inconsistent results with hormonal therapy, surgical treatment of cryptorchidism remains the gold standard.

Surgical Treatment

The first step of the surgical treatment of cryptorchidism is to re-examine the child under general anaesthesia. In 18% of the cases described as unpalpable during the examination in the office, the testicle will be felt under anaesthesia and will therefore change the surgical approach. The success rate of the surgical procedure depends mostly on the initial position of the testicle (*26*).

Palpable Testicle

Two different approaches can be utilized to perform the orchidopexy for a palpable testicle. The low (superficial inguinal pouch) and mobile palpable testis can be brought down by a scrotal (*27*) or an inguinal incision. The goal is to gain sufficient length to fix the testicle to the most dependant part of the scrotum without tension to the spermatic cord. The two manoeuvres that provide the greatest length for the cord to reach the scrotum are (*1*) the dissection of the cremasteric muscular fibres and any anomalous fibrotic attachments from the gonad and its cord, and (*2*) the separation of the patent processus vaginalis (which is anterior and medial to the cord) from the spermatic cord with high ligation of the hernia sac at the internal ring. If more length is required, for a higher undescended testicle, a retroperitoneal dissection is necessary to divide the lateral attachments to the spermatic vessels all the way to the lower pole of the kidney. These manoeuvres will release tension on the vessels and allow medial mobilization of the vessels to gain more length. Finally, a Prentiss manoeuvre whereby the testis and spermatic cord are transposed medial to the inferior epigastric vessels will create the most direct course toward the scrotum (*28*). This requires incision of the floor of the inguinal canal and can usually be accomplished without division of the inferior epigastric vessels contrary to the classic description of the manoeuvre. The inguinal approach is successful in bringing the testis down in most children less than 18 months of age. As the child grows older and longer or in cases where the testis is in a higher position, the inguinal approach may be more challenging and a laparoscopic approach may be helpful in facilitating the retroperitoneal dissection by improving visualization, while reducing morbidity to the child by avoiding the larger Gibson type extension of the inguinal incision.

The testicular arteries and veins are often the limiting factors to allow sufficient length to bring the testicle completely to the most dependant part of the scrotum. A one or two-stage Fowler-Stephens procedure has been advocated for these situations. Following ligation and division of the spermatic vessels, the testicle becomes dependant on the collateral circulation provided by the deferential and cremasteric vessels. Testicular mobilization can then be performed in one or two stages, as described by Fowler and Stephens (*29*). The ideal candidates for the one-stage orchidopexy are those presenting with a long looping vas. However, the blood supply provided by the collaterals should be tested before deciding if the procedure can be safely accomplished in one stage. A single stage procedure should not be attempted in the presence of vasal atresia or skeletonized cord. The two-stage procedure (with 3–6 months between ligation of the spermatic vessels and subsequent mobilization) permits better development of collateral vessels since no dissection of the vas or cremasteric structures is performed in the first stage.

To fix the testicle, a new channel from the inguinal incision toward the scrotum is created by blunt dissection with a finger. A transverse mid-scrotal

incision is made and a superficial dartos pouch is created. Placement of the testis in a dartos pouch results in complete circumferential adherence of the tunica albuginea to the pouch and prevents further displacement of the testicle. Deep transparenchymal suture insertion creates an extensive inflammatory reaction that may cause parenchymal damage. A superficial suture just into the tunica albuginea may be less harmful. Systematic testicular biopsies at the time of the orchidopexy are unnecessary and do not have a predictive value of future fertility or cancer development. Biopsies should be restricted to abnormal gonads, patients with ambiguous genitalia or abnormal karyotype.

During the physical examination in the office or under general anaesthesia, an atrophic testis (nubbin) can be palpated. This finding generally results from failure of gonadal organogenesis or from a prenatal vascular event. A scrotal approach can be used to remove the nonfunctional testis and to confirm it by histology. Studies have described as much as 14% of viable germ cells in nubbins with a theoretical risk of neoplasia (*30*). The presence of monorchidy secondary to a possible testicular torsion should raise questions about the necessity to fix the controlateral testicle. No evidence for nor against the fixation of the controlateral side has been published. However, the possible risk of torsion of a solitary testis should be weighted against the risk of trauma to that gonad during its fixation. The insertion of a testicular prosthesis has been advocated in childhood to minimise the psychological impact. However, this prosthesis will have to be upsized with growth of the child.

Nonpalpable Testicle

The laparoscopic approach for the diagnosis and treatment of a nonpalpable testicle is becoming more and more popular. The first port is placed in the umbilicus to introduce a camera and to evaluate the anatomy, principally the relation between the internal inguinal ring, the vas deferens, the spermatic vessels, and the testicle. Four different possible outcomes may be encountered during diagnostic laparoscopy for the undescended testicle. First, true testicular agenesis should prompt renal evaluation. Second, blind-ending vessels and vas deferens above the internal inguinal ring are indicative of a vanished testis and no further intervention is necessary except, maybe, scrotal fixation of the controlateral gonad. Third, the vessels and vas deferens can be observed entering a patent internal ring. This finding is compatible with either a viable or an atrophic testicle, and then an inguinal exploration should be performed to pex a viable gonad or remove a nubbin. Finally, an intra-abdominal testicle may be found, the management of this testis depends on the age at presentation and whether it is normal in size.

The abnormal or the atrophic intra-abdominal testicle in the older child (>10 years old) should be removed and an orchidopexy should not be attempted. Orchiectomy should also be performed if an intra-abdominal

gonad is present in a post-pubertal male with a controlateral normal testis. A normal testicle found within two centimetres proximal to the inguinal ring can be mobilized and placed in the scrotum in one procedure, using an open or a laparoscopic technique. If the laparoscopic approach is chosen, two trocars are introduced laterally to the umbilicus in the mid-clavicular line. The dissection of the spermatic cord is completed intraperitoneally and the mobilization may be carried out as high as the kidney. It has been proposed that at the end of the dissection if the testicle can be moved freely across to the controlateral internal ring, it is an indication that adequate length has been achieved to bring the testis down to the scrotum without tension. A dartos pouch is created and the testicle is passed in the scrotum with a hemostat or an additional trans-scrotal port. Control traction should be used to mobilize the testicle toward the scrotum in order to avoid accidental testicular avulsion. Excessive tension may also cause ureteric obstruction if the dissection was inadequate. A staged procedure should be planned if the testicle is more proximally located and the decision should be made relatively early during the surgery to limit the dissection and to permit the growth of collateral vessels. The second procedure is usually planned after 6 months and can be performed laparoscopically or by open technique. Ultimately, testicular auto-transplantation of the testis to the inferior epigastric vessels can be performed if microsurgical expertise is available. This is probably the most appropriate technique for a solitary, high intra-abdominal testicle for which even a low risk of atrophy after a two-stage Fowler-Stephens procedure is unacceptable.

COMPLICATIONS OF ORCHIDOPEXIES

Infection and bleeding with scrotal hematoma are possible complications following an orchidopexy. Laparoscopic approaches also involve all potential complications associated with insertion of trocars and pneumoperitoneal insufflation. More specific complications related to an orchiectomy or an orchidopexy are injury to the ilio-inguinal nerve, vas deferens or spermatic vessels, iatrogenic or spontaneous testicular torsion, testicular retraction, and testicular atrophy. Gonadal atrophy may result from torsion of the spermatic cord, extensive electrocoagulation with vascular thrombosis, excessive traction on the cord, ligature of the blood supply, or compression of the vessels by an abscess or a hematoma. Late testicular atrophy is also possible for a patient that underwent previous treatment for undescended testis after a vasectomy if the spermatic vessels were injured and the testicular blood supply was dependent on the deferential artery.

CONCLUSION

The undescended testis is a frequent cause for consultation in the newborn male. The spontaneous descent after birth usually happens in the

first 3 months of life and is essentially inexistent after 1 year of age. The treatment should be planned around 6–12 months to decrease the risks of histological changes and to prevent further complications. The surgical approach is planned according to the physical exam performed in the office and under general anaesthesia at the time of the repair. Preoperative radiological evaluation should not be routinely performed since it does not provide accurate information due to a high rate of false-positive and false-negative studies and does not eliminate the need for surgical exploration. Different surgical techniques may be used with high success rates. Nonetheless, basic principles in testicular mobilization and tissue handling should be respected to avoid complications.

REFERENCES

1. Cisek LJ, Peters CA, Atala A, Bauer SB, Diamond DA, Retik AB. Current findings in diagnostic laparoscopic evaluation of the nonpalpable testis. J Urol 1998;160(3 Pt 2):1145–9; discussion 50.
2. Virtanen HE, Toppari J. Epidemiology and pathogenesis of cryptorchidism. Hum Reprod Update 2008;14(1):49–58.
3. Cryptorchidism: a prospective study of 7500 consecutive male births, 1984–8. John Radcliffe Hospital Cryptorchidism Study Group. Arch Dis Child 1992;67(7):892–9.
4. Wenzler DL, Bloom DA, Park JM. What is the rate of spontaneous testicular descent in infants with cryptorchidism? J Urol 2004;171(2 Pt 1):849–51.
5. Mayr JM, Lawrenz K, Berghold A. Undescended testicles: an epidemiological review. Acta Paediatr 1999;88(10):1089–93.
6. Cortes D, Thorup JM, Visfeldt J, Schwartz M. Is infertility after surgery for cryptorchidism congenital or acquired? Pediatr Surg Int 1998;14(1-2):6–8.
7. Chilvers C, Dudley NE, Gough MH, Jackson MB, Pike MC. Undescended testis: the effect of treatment on subsequent risk of subfertility and malignancy. J Pediatr Surg 1986;21(8):691–6.
8. Lugg JA, Penson DF, Sadeghi F, et al. Prevention of seminiferous tubular atrophy in a naturally cryptorchid rat model by early surgical intervention. J Androl 1996;17(6): 726–32.
9. Abratt RP, Reddi VB, Sarembock LA. Testicular cancer and cryptorchidism. Br J Urol 1992;70(6):656–9.
10. Taran I, Elder JS. Results of orchiopexy for the undescended testis. World J Urol 2006;24(3):231–9.
11. Dieckmann KP, Skakkebaek NE. Carcinoma in situ of the testis: review of biological and clinical features. Int J Cancer 1999;83(6):815–22.
12. Jones BJ, Thornhill JA, O'Donnell B, et al. Influence of prior orchiopexy on stage and prognosis of testicular cancer. Eur Urol 1991;19(3):201–3.
13. Pettersson A, Richiardi L, Nordenskjold A, Kaijser M, Akre O. Age at surgery for undescended testis and risk of testicular cancer. N Engl J Med 2007;356(18):1835–41.
14. Moller H, Skakkebaek NE. Risks of testicular cancer and cryptorchidism in relation to socio-economic status and related factors: case-control studies in Denmark. Int J Cancer 1996;66(3):287–93.
15. Riegler HC. Torsion of intra-abdominal testis: an unusual problem in diagnosis of the acute surgical abdomen. Surg Clin North Am 1972;52(2):371–4.
16. Elder JS. Epididymal anomalies associated with hydrocele/hernia and cryptorchidism: implications regarding testicular descent. J Urol 1992;148(2 Pt 2):624–6.
17. Elert A, Jahn K, Heidenreich A, Hofmann R. [The familial undescended testis]. Klin Padiatr 2003;215(1):40–5.

18. Eijsbouts SW, de Muinck Keizer-Schrama SM, Hazebroek FW. Further evidence for spontaneous descent of acquired undescended testes. J Urol 2007;178(4 Pt 2):1726–9.
19. Huff DS, Snyder HM, 3rd, Hadziselimovic F, Blyth B, Duckett JW. An absent testis is associated with contralateral testicular hypertrophy. J Urol 1992;148(2 Pt 2):627–8.
20. Stec AA, Thomas JC, DeMarco RT, Pope JCt, Brock JW, 3rd, Adams MC. Incidence of testicular ascent in boys with retractile testes. J Urol 2007;178(4 Pt 2):1722–4; discussion 4–5.
21. Hrebinko RL, Bellinger MF. The limited role of imaging techniques in managing children with undescended testes. J Urol 1993;150(2 Pt 1):458–60.
22. Cain MP, Garra B, Gibbons MD. Scrotal-inguinal ultrasonography: a technique for identifying the nonpalpable inguinal testis without laparoscopy. J Urol 1996;156(2 Pt 2): 791–4.
23. Hadziselimovic F, Herzog B. Treatment with a luteinizing hormone-releasing hormone analogue after successful orchiopexy markedly improves the chance of fertility later in life. J Urol 1997;158(3 Pt 2):1193–5.
24. Polascik TJ, Chan-Tack KM, Jeffs RD, Gearhart JP. Reappraisal of the role of human chorionic gonadotropin in the diagnosis and treatment of the nonpalpable testis: a 10-year experience. J Urol 1996;156(2 Pt 2):804–6.
25. Pyorala S, Huttunen NP, Uhari M. A review and meta-analysis of hormonal treatment of cryptorchidism. J Clin Endocrinol Metab 1995;80(9):2795–9.
26. Docimo SG. The results of surgical therapy for cryptorchidism: a literature review and analysis. J Urol 1995;154(3):1148–52.
27. Dayanc M, Kibar Y, Irkilata HC, Demir E, Tahmaz L, Peker AF. Long-term outcome of scrotal incision orchiopexy for undescended testis. Urology 2007;70(4):786–8; discussion 8–9.
28. Prentiss RJ, Weickgenant CJ, Moses JJ, Frazier DB. Surgical repair of undescended testicle. Calif Med 1962;96:401–5.
29. Fowler R, Stephens FD. The role of testicular vascular anatomy in the salvage of high undescended testes. Aust N Z J Surg 1959;29:92–106.
30. Storm D, Redden T, Aguiar M, Wilkerson M, Jordan G, Sumfest J. Histologic evaluation of the testicular remnant associated with the vanishing testes syndrome: is surgical management necessary? Urology 2007;70(6):1204–6.

12 Acute Scrotum

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Abstract Boys of any age may develop acute scrotal pathology. Due to the potential for testicular loss, torsion of the spermatic cord is always a diagnostic consideration. The goals of this chapter are to review the causes of the acute scrotum, define the appropriate diagnostic evaluation, advise criteria for referral, and outline reasoned management.

Keywords Acute scrotal swelling · Scrotal pathology in the neonate

EMBRYOLOGY AND NORMAL DESCENT

A basic understanding of the development and normal anatomy of the testicles and the scrotum leads to an appreciation of the pathology of the acute scrotum. The development of the testicles, as well as the gubernaculum, begins in the seventh week of gestation. The gubernaculum encases the epididymis and lower pole of the testis, extends into the inguinal canal, and maintains its fixation to the testis. Approximately 75% of testicles descend through the inguinal canal between 24 and 28 weeks of gestation (*1*). By 30 weeks of gestation nearly all testicles have made it into the scrotum (*1*). In its final location in the scrotum, the epididymal head lies along the superior pole of the testis and its body and tail extend toward the inferior pole and lateral.

FIRST RULE OUT TORSION

The evaluation of an acute scrotum needs to be approached in a timely fashion. All cases must be suspected of acute spermatic cord torsion as there is an established need for rapid diagnosis and management (*2*). Evaluating

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the child as soon as possible, after the onset of symptoms, will help in establishing an accurate diagnosis, and may be pertinent to salvage of the testicle (*3*).

Unfortunately, timely presentation of an acute scrotum is patient dependent and many times the diagnosis is obscured by delayed evaluation. When symptoms have been present for several days, the scrotum is often markedly indurated, swollen and tender. Intrascrotal contents may not be easily identified via palpation and diagnosis is often equivocal. In these cases additional imaging should be obtained as quickly as possible. The concept of exploration for equivocal scrotal pathology is a changing paradigm. With an early physical exam and the advances of minimally invasive imaging, many etiologies can be successfully diagnosed without surgical exploration (*4*).

The consultant, based on clinical history and physical examination, can often rule out testicular torsion without the need for diagnostic studies. Imaging is time consuming, costly, and may not effect final management; thus, each case should be considered individually prior to routine imaging (*5*–*8*).

History should include age of the patient and the duration of the symptoms. Make sure to ask about similar episodes in the past, history of surgery, urinary symptoms, and trauma to help aid in a diagnostic plan.

Typically the child with testicular torsion will be experiencing severe pain unrelieved by ice, position, or over the counter analgesics (*2*). A history of nausea and vomiting are common and testicular retraction may be found on examination. The consultant can proceed to contact the operating room and anesthesiology staff to prepare for surgery (*2*). A complete blood count can be ordered but is not essential with classical findings. While the most time critical urologic cause of acute scrotal discomfort is testicular torsion, other common etiologies must be considered (*3*). These include torsion of a testicular or epididymal appendage, trauma, infection, hydrocele, and incarcerated inguinal hernia (*2*). Other more rare conditions include Henoch-Schönlein purpura, acute appendicitis, acute leukemia, idiopathic scrotal edema, and testicular tumor.

TAKING A COMPLETE HISTORY

The age of the child may help to suggest a diagnosis. For example, testicular torsion is seen most often during puberty (males ages 10–19) and second most commonly in the newborn (*3*). Epididymo-orchitis tend to occur in the post-pubertal male (*9*–*11*). Torsion of the testicular appendage is typically a pre-pubertal event (*12*–*14*).

It is important to ask about recent trauma to the testicle, for example, enquiring about sports related injuries to the inguinal canal or scrotum. Direct trauma to the testicle can cause acute scrotal swelling (*11*, *15*). Trauma has also been listed as an etiology for testicular torsion in 4–8%

of cases, though recall bias may a component of this statistic (*8*). A history of trauma does not rule out torsion of the testicle or its appendages.

Make sure to ask about any delay in descent of the testicles or hydrocele that may have been present at birth or in early childhood. A suspected patent processus vaginalis or problem with descent should lead one to consider how well the testicles are fixed to the scrotum (*1*).

Surgical history is important for it is possible that inguinal surgery may fix the cord structures in place through post-operative scarring (*2*). A history of an inguinal herniorrhaphy, a common pediatric operation, may make testicular torsion less likely, but the literature reports torsion following inguinal herniorrhaphy as well as orchidopexy (*2*). Ask about any recent scrotal or inguinal surgery in evaluating for a possible post-operative infection. Swelling alone is likely part of the healing process, but if accompanied by erythema and purulent drainage, the likelihood of an infectious process increases.

Obtain a history of the duration, severity and frequency of the pain. It can also be helpful to ask the parents about their perception of the child. Is the child typically stoic, or is he overly emotional concerning small injuries? One can easily be fooled by a child who does not want to admit severe pain as to invite intervention or appear weak of character. Also enquire whether the patient has experienced similar episodes of testicular pain in the past. Acute onset and resolution of testicular pain may indicate a torsion/detorsion scenario (*2*). Alternatively, a history of gradually increasing testicular pain over a week with slowly increasing swelling and discomfort leads to consideration of torsion of a testicular or epididymal appendage or epididymitis (*9*).

Finally, ask about accompanying systemic symptoms such as fevers, nausea, vomiting, abdominal pain, and recent viral illness. Include questions about urinary symptoms such as pain with urination, blood in the urine, increased urinary frequency or urgency, and the color of the urine. This will help in your differential of an infection, ischemic process, or referral of pain from an abdominal source (*2*, *16*).

THE PHYSICAL EXAM

Physical exam findings are an important part of the initial assessment. To obtain the best results possible, one must consider the general setting in which the examination is performed. Emergency rooms tend to have a high level of activity. Prior to starting your examination, try to secure a quiet or private room. The surrounding temperature should be warm to allow for scrotal relaxation. Keep in mind that the patient likely has a high degree of discomfort and anxiety. Reassure the child with a calm voice and gentle touch. Try to limit the number of examinations performed on the child. Ideally, the consultant would be one of the first to perform the examination. The boy is much more likely to cooperate if he has not had to endure multiple uncomfortable examinations. When beginning your physical exam, start

away from the scrotum, which is the most tender area. This will allow the child to relax somewhat and gain your trust.

Remember that it is important to perform the physical exam in the appropriate order (*2*, *6*). The first step is close observation followed by abdominal palpation, which is often comforting as it is familiar and non-threatening. Next attempt to elicit a cremasteric reflex. Observe the scrotal skin, place the examining hands in position to cradle the general area of the testis; then slowly allow your fingertips to discern the position, shape, size, and consistency of the testis, and the specific location of any pain without any sudden movement or significant pressure. Palpate the lower pole of the testicle and epididymis, and finally the upper pole and spermatic cord, beginning with the asymptomatic side.

General Appearance:

- Observe the patient's overall activity level and facial expression to help gauge the severity of the pain.
- A child who is lying very still indicates severe pain associated with movement. A child that is walking around the emergency room without difficulty is reassuring.
- Looks for signs of systemic illness such as flushing from fever.

Abdominal Exam:

- Palpate the abdomen, looking for tenderness or masses.
- Intra-abdominal pathology can present as acute scrotal pain (*16*).
- Perforated appendicitis can present as acute onset of right side testicular pain and swelling from purulent drainage entering a patent processus vaginalis.
- Palpate the inguinal canals to evaluate for an incarcerated hernia. Finding a thickened intracanalicular spermatic cord is suggestive of this pathology.

Scrotal Exam:

- Palpate the skin to assess the degree of induration, erythema, and tenderness.
- A relaxed hemiscrotum is reassuring of a less severe process.
- A retracted testicle indicates pain and possibly testicular torsion.
- Abnormal position of the testicle (e.g., horizontal lie) can similarly be a telling sign of torsion.
- The degree of scrotal swelling and erythema correlates with the degree of inflammation and can give an idea of the time frame prior to presentation.
- Try to elicit a cremasteric reflex by stroking the skin on the inner thigh. This technique should first be attempted on the uninvolved side, giving you a baseline reflex for comparison. Eliciting a cremasteric reflex on the involved side suggests against testicular torsion.

Testicular Exam:

- Palpate the uninvolved side first to reassure your patient and have a baseline for comparison.

- Examine the lower pole of the testis and epididymis prior to examining the upper pole.
- If the lower pole of the testis and epididymis is non-tender and normal in size, testicular torsion is unlikely.
- The majority of testicular and epididymal appendages are located in the upper pole (*13*). When you palpate the upper pole of the testis and epididymis, try to feel for an infarcted appendage. This may feel like a small, firm nodule that is extremely tender.
- Sometimes the infarcted appendage can be seen through the skin (blue dot sign).

Once finished with your history and physical examination, you may diagnose testicular torsion and proceed to management. However, many times your clinical diagnosis is equivocal and further tests may be needed. Below we elaborate on the differential of the acute scrotum with the appropriate diagnostic imaging and treatment.

TORSION OF THE SPERMATIC CORD

Testicular torsion is defined as a twisting of the testis and spermatic cord. This results in obstruction of venous return from the testis, which then leads to equalization of venous and arterial pressure (*8*). Arterial flow to the testicle is consequently compromised and ischemia occurs. Rarely acute arterial occlusion may occur.

Testicular torsion occurs in 1 of 4000 males before the age of 25 and makes up 25–35% of the acute scrotal diagnosis in the pediatric population (*8*). This event is biphasic in incidence and is seen most often during puberty (males ages 10–19) (*3*). It is seen second most commonly in the newborn, which will be discussed later.

The patient may have a history of delay in descent of the testicles or hydrocele that may have been present at birth or in early childhood. A suspected patent processus vaginalis or problem with testicular descent should lead one to consider how well the testicles are fixed to the scrotum (*1*). A malformation of the tunica vaginalis is responsible for the classic "bell-clapper" deformity. This is when the tunica vaginalis completely encircles the epididymis, distal spermatic cord, and the testis instead of attaching to the posterolateral aspect of the testis (*8*). This malformation, which is reported in 90% of cases, allows the testis to rotate freely resulting in torsion (*8*). Additionally, oblique insertion of cremasteric fibers on the spermatic cord may contribute to the tendency to twist.

The degree of ischemia largely depends on the length of time the testicle remains twisted. Testicular salvage rate is around 90% when detorsion is performed within 6 hours or less from the onset of symptoms (*8*). This rate however falls to 50% at 12 hours and the testicle is almost always unsalvageable at 24 h (*8*). Unfortunately, many times the patient presents

to the physician after a significant delay. One study found that 85% of males did not think it was necessary to seek medical attention for testicular swelling (*3*). In another study, more than half of the patients with acute onset of testicular pain delayed seeking medical help for 12 or more hours (*3*).

Testicular torsion typically presents as acute onset of unilateral testicular pain and tenderness. Often times there are associated nausea, vomiting, scrotal erythema, and scrotal edema (*5*). However, one study did not show any of these symptoms to be statistically significant is distinguishing between torsion and other etiologies of the acute scrotum. Pain can be referred to the inguinal canal on the symptomatic side or the lower abdomen. The patient may give a history of similar episodes that spontaneously resolved, indicating a torsion/detorsion picture (*2*). It is important to remember that a history of trauma or the lack of severe pain does not rule out torsion.

On physical exam, the involved testis is higher lying in the scrotum and swollen. This is due to shortening of the spermatic cord as it twists. Absence of a cremasteric reflex is the most sensitive physical exam finding for testicular torsion but unfortunately not specific to torsion alone (*2*). Sometimes the testicle will have a transverse lie. It will be tender to palpation and feel firmer compared to the asymptomatic side. Many times, if the torsion has been present for several hours the amount of inflammation will make testicular landmarks difficult to distinguish.

If torsion is diagnosed based on the clinical presentation and physical exam findings and you are unable to detorse the testicle at bedside, then the patient should undergo emergent surgical exploration. In cases where suspicion of torsion is low or equivocal, diagnostic imaging is recommended (*4*, *14*). If imaging is not available in an equivocal case, the patient should undergo surgical exploration.

Color Doppler ultrasonography is one of the most commonly used diagnostic modalities. It has become the imaging study of choice due to availability and experience. This technique can visualize intratesticular blood flow and is 80–100% sensitive and 90–100% specific (Fig. 12.1) (*4*, *14*). The range is likely due to operator dependency. In cases of torsion, the testis will have absent or decreased blood flow (Fig. 12.2). Ultrasound has the additional benefit of being able to distinguish between testicular and extratesticular disease.

Scintigraphy with technetium 99m pertechnetate can also be used to diagnose testicular torsion. It is nearly 100% sensitive for testicular torsion (*6*). A torsed testis will have decreased delivery of radiotracer, indicating diminished or absent blood flow. This diagnostic modality is often not practical for use in the acute setting as the isotope must be prepared at the time of request and is not readily available. In addition, its clinical value is often less than that of color Doppler ultrasound since it does not provide anatomic data. We have used this test for delayed presentation of torsion to document the fate of the testis when needed to encourage surgical exploration.

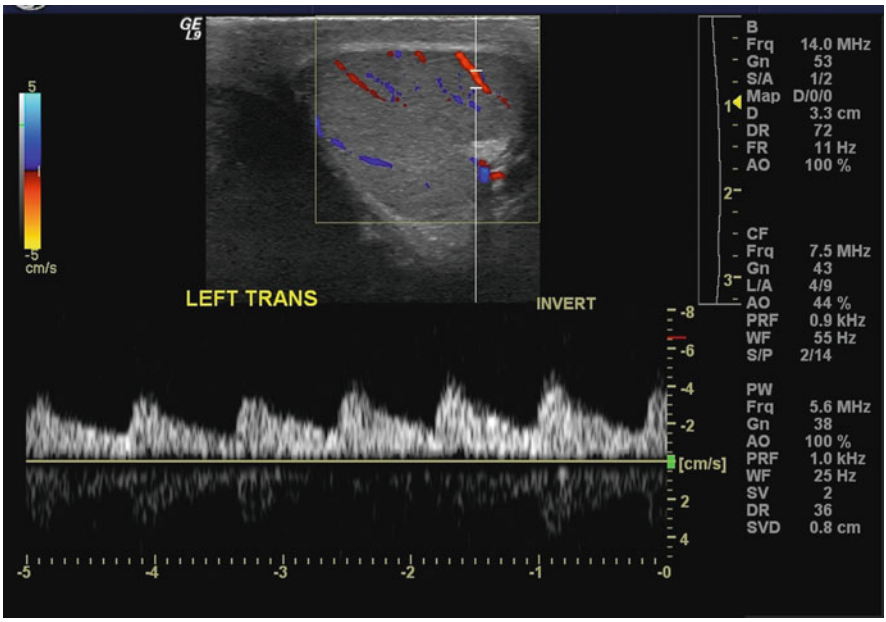

Fig. 12.1. Doppler ultrasound of the *Left* testicle. Testicular size measures 4.0 × 2.4 × 1.9 cm. The testicle is normal in appearance, homogeneous, and has no reactive hydrocele. There is normal vascular flow.

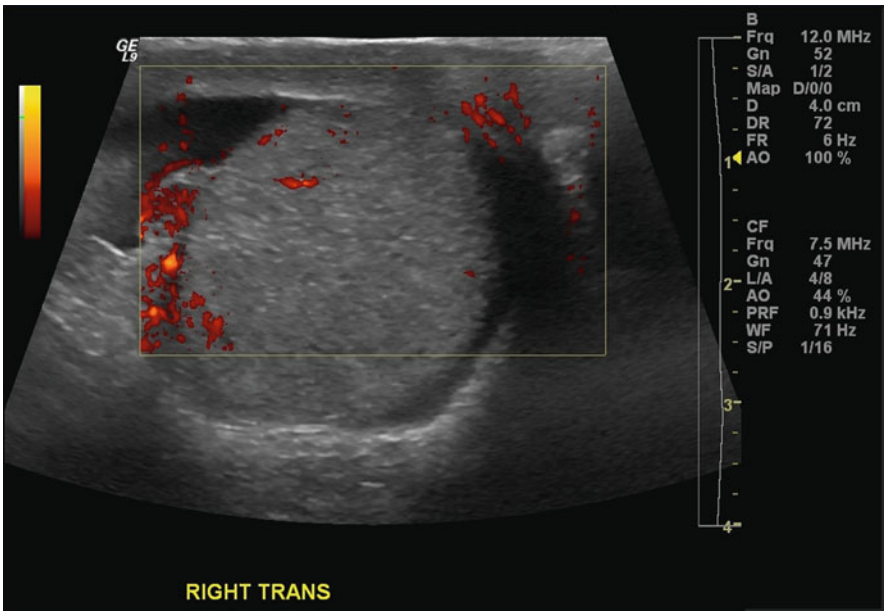

Fig. 12.2. Doppler ultrasound of the *Right* testicle. Testicular size measures 3.8 × 2.4 × 2.4 cm. The testicle is heterogeneous, with an enlarged epididymis, and a reactive hydrocele is present. Vascular flow is absent.

Surgical exploration and detorsion are mandatory in all cases of testicular torsion. However, one can attempt manual detorsion at bedside to allow relief of symptoms and immediate restoration of blood flow (Fig. 12.3). In two-thirds of the cases of testicular torsion, the testis has rotated medially, when examining the patient from an anterior point of view (*7*). Therefore, your first attempt should be to rotate the testis laterally within the scrotal sac (think of opening a book). The maneuver is accomplished by grasping the testis in the fingertips of both hands to achieve a 180-degree rotation. This movement initially causes pain and a spermatic cord block can be performed first, but is not always necessary. If you are successful the testicle will stay easily in its new position and there will be more length on the spermatic cord. Further rotation should be attempted in similar increments until the testis assumes an appropriate position in the scrotum. The patient will report immediate improvement of pain after a few moments of restored blood flow. If attempted lateral detorsion fails to achieve improvement in testicular position, try the same technique but medially. Manual detorsion has been reported to have a 26–80% success rate (*7*, *8*).

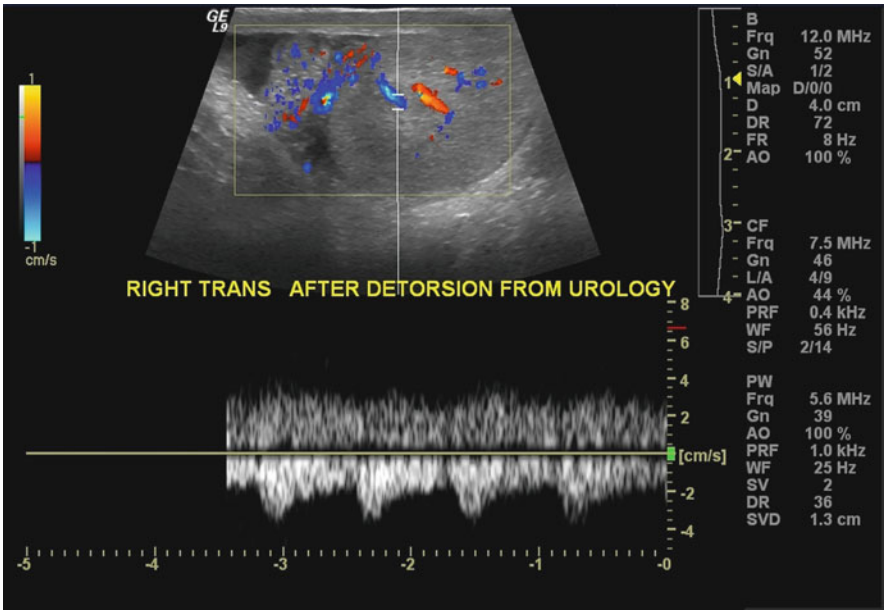

Fig. 12.3. Repeat imaging after manual detorsion at bedside demonstrates presence of spectral Doppler flow within the right testis as well as the epididymis.

Even if manual detorsion is successful the patient will still require a surgical exploration for final correction and possible orchidopexy versus orchiectomy. Both testes should be explored since the anatomic abnormality that allowed the torsion is likely present on the contralateral side (*2*). If the torsed testis is not viable, remove it without an attempt at detorsion. If it

appears viable, return the testis to its normal anatomic position and perform an orchidopexy using non-absorbable suture. Make sure to fix both testicles in place at three points (laterally on each side and inferiorly).

The infertility risk in patients with prior testicular torsion has not been well established. If the patient has a normal, uninvolved testis at the time of surgery, then normal fertility is more likely (*2*). All patients will require long-term follow up to assess for testicular atrophy.

TORSION IN THE NEONATE

Neonatal torsion has been reported as making up 12% of all cases of torsion (*17*). Most cases of neonatal torsion are extravaginal, meaning there is torsion of the entire spermatic cord including the tunica vaginalis and internal spermatic fascia (*18*). This is related to the loose attachment the latter conveys to the scrotum at the time of birth (*1*).

One must differentiate between prenatal torsion, in which testicular salvage is impossible compared to neonatal torsion, where there is a chance for testicular salvage. Unfortunately, most cases of torsion in the neonate are in fact prenatal (*17–20*).

Testicular torsion presents differently in the neonate compared to classic torsion that occurs in the peripubertal boy. The presentation is typically asymptomatic and has an uncertain time of onset (*17*). Most cases are discovered incidentally during routine examination of the newborn at the time of birth. These cases of torsion are prenatal and the testicle are not salvageable (*17*, *18*). The picture can become more difficult when the torsed testicle is not picked up at birth but rather found several hours later in the nursery. This delay in diagnosis raises the question whether there was a true observed change in exam versus a missed diagnosis of prenatal torsion. Simply exploring all cases of suspected torsion is not acceptable given the risk of general anesthesia in the neonate and the low chance for testicular salvage (*17*, *18*). In cases of a "missed torsion" color Doppler ultrasound is useful and should be done acutely for purposes of documentation and final management (*17–19*). A missed prenatal torsion will have no blood flow to the testis on color Doppler ultrasound. MRI and scintigraphy with technetium 99m pertechnetate can also be used to confirm testicular loss (*6*). Make sure to document testicular loss confirmed by imaging as well as the condition of the contralateral testis. Also document thorough discussion of the findings and management. The majority of cases in the literature have been reported as unilateral. However, a recent article on perinatal testicular torsion showed a 22% (4/18) overall incidence of asymptomatic contralateral torsion discovered at the time of surgical exploration (*20*). If there is any question about the integrity of the contralateral testis, emergent surgical exploration should be performed to try to salvage the contralateral testis. If the torsion is prenatal and the contralateral testis is intact, the torsed testis can be treated with orchiectomy or observation in a non-emergent fashion

(*17*). Some authors recommend exploration for contralateral orchidopexy as their preferential management (*20*).

Recommendations regarding testicular torsion in the neonate have been varied. One issue is the lack of testicular preservation reported in the literature. The ischemic time frame for rescuing the testicle is less than 4 h (*7*, *17*). Most cases of prenatal torsion are unobserved and thereby the window of opportunity has passed. Cases of neonatal torsion that are observed should be operated on emergently, as testicular preservation can be achieved.

Despite the low success rate, there have been cases reported in the literature of testicular preservation of endocrine function after long periods of ischemia (*17*). Therefore the majority of testis should be left in place if exploratory surgery is performed. The exception is in cases of obvious liquefaction necrosis, which should result in removal of the testis. Interestingly, there have not been any reported cases of intolerance of a retained ischemic testicle (*17*).

The timing of surgical exploration is also an issue. The stress of anesthesia in the first 24–48 h of life can interfere with the transition from fetal to extrauterine circulation (*17*). The immaturity of the patient's central nervous system can also lead to difficulty in regulating cardiac and pulmonary function. Delay of surgery or use of local or regional anesthetic may be necessary to minimize risk to the neonate. If the hospital has little experience with neonatal surgery, transfer to a larger center may be advisable.

TORSION OF THE TESTICULAR OR EPIDIDYMAL APPENDAGE

A testicular appendage is a remnant of the paramesonephric duct, whereas the epidydimal appendage is a remnant of the mesonephric duct. Both of these structures are highly prevalent in the pediatric population and are located near the head of the epididymis (*14*). Torsion of a testicular or epididymal appendage is a common cause of the acute scrotum in the pediatric population (*12*).

It is often difficult to distinguish between a testicular torsion and torsion of a testicular appendage. Both will present with acute onset of scrotal pain and swelling. However, a patient who has torsion of the appendix testis will be less likely to have systemic symptoms such as nausea, vomiting or fever (*5*). The pain is typically less severe in nature and progresses slowly over 2–3 days. Urinalysis will be negative.

On physical exam, the scrotum will be swollen, but the testicles should be comparable in size. Testicular tenderness will be localized to the upper pole of the testicle near the head of the epididymis early in the course. The testicle should have normal position in the scrotum. Sometimes a hard, tender nodule 2–3 mm in diameter can be palpated near the upper pole of the testicle. If the scrotal skin is thin enough, this nodule may appear darker giving

the classic "blue dot sign." These patients should have a cremasteric reflex on the symptomatic side.

In cases where there is low suspicion for testicular torsion, one can confirm the diagnosis with color Doppler ultrasound (*14*). This technique will evaluate volume, echogenicity, texture, and blood flow of the testicle and epididymis. There will be increased blood flow to the epididymis and normal blood flow in both testicles. Echogenicity of the visualized appendage is reported as varied in the literature. A reactive hydrocele is a common finding. Torsion of a testicular/epididymal appendage is diagnosed by ultrasound finding of an extratesticular, hypovascular structure, often with hyperemia in the surrounding paratesticular region (Fig. 12.4). One paper reported 100% specificity using color Doppler ultrasound to confirm torsion of testicular appendages larger than 5.6 mm (*14*).

If there is any uncertainty about testicular torsion then the patient should undergo an emergent surgical exploration. If the history, physical exam, and ultrasound findings (if performed) are consistent with torsion

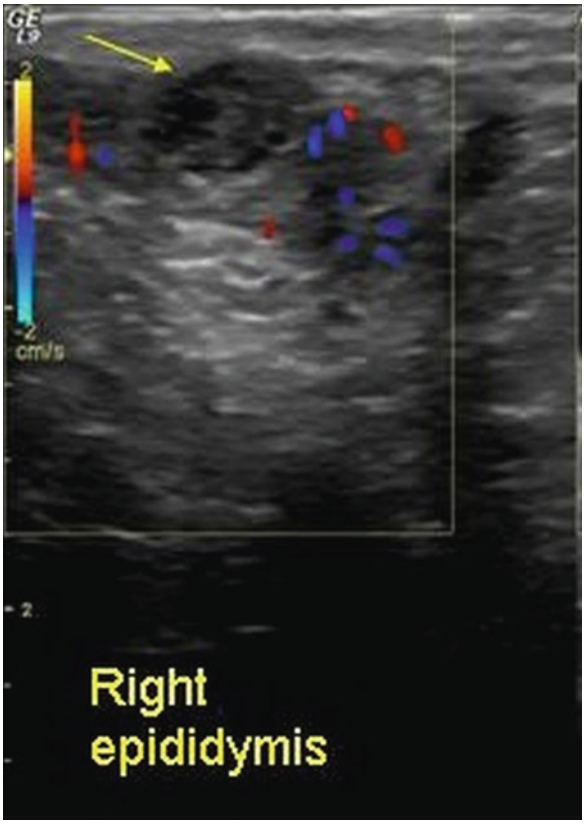

Fig. 12.4. Hypovascular lesion (*arrow*) with reactive hyperemia is classic for torsion of the appendix testis or epididymis.

of the appendix testis then the treatment is palliative. Recommend scrotal elevation, bed rest, and scrotal support to help with the swelling. Anti-inflammatories and analgesics can be used for pain management. Explain to the parents that the swelling will often get worse before it gets better. Sudden edema 3–5 days after onset of pain is very commonly seen. Scrotal edema and tenderness can last several weeks and is directly correlated with degree of activity.

EPIDIDYMITIS

Epididymitis is defined as inflammation of the epididymis. This is a rare condition in prepubertal boys, though one article did report the incidence to be as high as 28% (*10*). Epididymitis is the most common etiology of acute scrotal swelling in the sexually active male (*9*, *11*). In the pediatric population, 20–80% of cases are associated with urinary tract infections (*9*). In addition, up to 50% of cases are associated with an anatomic abnormality of the genitourinary or lower gastrointestinal tract (*9*). There has also been an association with children who have dysfunctional voiding.

There are two types of epididymitis: bacterial and non-bacterial. Bacterial epididymitis is typically associated with urinary tract infection in prepubertal/non-sexually active males. In this group the most common organism is *Escherichia coli* (*9*). In sexually active males, *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are the most likely offenders (*9*). Notable exceptions include *Staphylococcus aureus* in patients with cystic fibrosis and Salmonella in patients with sickle cell disease (*9*). Non-bacterial epididymitis can be caused by a chemical inflammatory response from intrusion of sterile urine retrograde into the epididymis. High-pressure bladder storage or emptying, such as that seen in dysfunctional voiding, can cause this kind of reflux in boys. Bladder outlet obstruction, such as posterior urethral valves or stricture, can create the same problem. Viruses have also been shown to be a cause of epididymitis. Some children will present with a prior history of fevers and rash, which then leads to scrotal symptoms a few days later. An excellent example of this is mumps epididymo-orchitis.

The patient with epididymitis presents with scrotal pain that slowly increases in severity over several days. The pain is sometimes referred to the inguinal canal or abdomen. Other common symptoms include fever, urinary frequency and urgency, and dysuria (*9*, *10*). In the older, sexually active male there can be urethral discharge. Pyuria is commonly seen on urinalysis.

Make sure to ask about history of urethral instrumentation, catheterization or trauma, as these can lead to a urinary tract infection and thereby epididymitis. A history of hypospadias, anorectal malformation, or bowel/bladder elimination difficulty can be further clues.

On physical exam there is unilateral, upper pole testicular tenderness and tenderness at the head of the epididymis. Later in the clinical course the entire epididymis is swollen but the testis feels normal to palpation and has

a normal lie in the scrotum. The cremasteric reflex will be present. As time progresses so does scrotal swelling. The scrotal skin becomes erythematous and edematous and its appearance looks much like the skin of an orange. At this point it is difficult to distinguish intrascrotal landmarks. As a part of your physical exam, make sure to examine the spine and anus for any signs of occult abnormalities. Of note Prehn's sign, which is performed by lifting the scrotum to assess change in pain, is not helpful in differentiating between torsion and epididymitis (*9*).

Urinalysis and urine culture should be obtained when the differential diagnosis includes epididymitis. Urethral swabbing may be traumatic and is rarely helpful with diagnosis in the absence of other findings and is therefore not recommended (*9*). Often times a color Doppler ultrasound is obtained to rule out testicular torsion. The ultrasound will show increased blood flow to the affected epididymis, and normal or increased blood flow to the ipsilateral testis. In the prepubertal boy with a urinary tract infection, or in patients with recurrent episodes, further imaging may be needed (*9*, *10*). Following acute treatment, a voiding cystourethrogram is useful to evaluate the urethra. Upper tract imaging with either an ultrasound or intravenous urogram is also recommended to assess for ureteral ectopia (*9*).

As in other etiologies of acute scrotum, if testicular torsion is not ruled out, proceed to surgical exploration. Treatment is with anti-inflammatories, analgesics, and antibiotics (*9*). For non-sexually active males, cover for gram-negative urinary tract infection empirically. Make sure to follow up on the urine cultures and adjust your antibiotic choice accordingly. In addition, non-sexually active patients with documented UTI should be placed on prophylactic antibiotics until structural imaging is completed. For sexually active males, treat for bacterial epididymitis empirically using the CDC guidelines and encourage treatment of partners. All patients will benefit from scrotal elevation, scrotal support, and rest. It can take several weeks for symptoms and swelling to resolve completely.

TRAUMA

Testicular trauma is a common cause of acute scrotal swelling, bruising, and pain. Trauma can result in hematoma, hydrocele, or testicular fracture. Scrotal trauma is most common in males age 10–30, with the majority of cases being blunt trauma from sports related injuries (*15*). Patients with scrotal trauma typically present emergently and a rapid diagnosis is desirable to guide treatment. Ultrasound is ideal for assessment of scrotal trauma as it allows non-invasive evaluation of testicular integrity, blood flow, and scrotal contents (*15*). If the testis is fractured, the patient will require emergent surgery for closure of the tunica albuginea. Testicular salvage is reported at 80–90% of cases (*15*). Up to 50% of acquired hydroceles are from trauma (*15*). These, as well as hematoceles, tend to resolve on their own over time

and can be managed conservatively with observation. The patient should undergo exploratory surgery in the following cases:

- Tunica albuginea disruption is visualized.
- If the ultrasound findings are equivocal and there is high clinical suspicion for fracture.
- If there is intratesticular hemorrhage and ultrasound is unable to visualize the fully intact tunica albuginea.
- If the tunica appears intact on ultrasound but there is intra and extratesticular hemorrhage.

When exploring for a suspected testicular fracture, initial evacuation of the hematocele may not reveal an apparent fracture. A common site to find a tear in the tunica albuginea is posterior at the root of the mediastinum testis hidden by an adherent epididymis. Always use an absorbable suture to close the fracture.

IDIOPATHIC SCROTAL OEDEMA

This is an uncommon cause of acute scrotal swelling. The clinical presentation is acute onset of scrotal swelling and erythema, which is sometimes bilateral. However, this condition differs from other causes of acute scrotal pathology in that it is painless and non-tender to palpation (*11*). The testicles will be palpable and the swelling is not reducible, as seen in an inguinal hernia. It has also been proposed to occur as part of an allergic reaction (*11*).

ACUTE SCROTAL HYDROCELE

Acute scrotal hydrocele occurs from abdominal fluid entering the scrotal sac via a patent processes vaginalis during straining (*2*). This form of acute scrotal swelling is often pre-pubertal and may be seen after acute distress from intra-abdominal pathology or coughing. The scrotum is non-tender to palpation. Color Doppler ultrasound will be negative for testicular torsion and a hydrocele will be evident. This can be managed on an elective basis.

HENOCH-SCHÖNLEIN PURPURA

Although rare, acute scrotum can be the initial presenting manifestation of Henoch-Schönlein purpura (*21*). This is a syndrome characterized by systemic vasculitis of unknown cause. The patient will have non-thrombocytopenic purpura as well as skin, joint, intestinal and renal involvement. Involvement of the male genitalia has been reported in 2–38% of cases in the literature (*21*). The patient develops bilateral, ecchymotic scrotal swelling that is painful. Color Doppler ultrasound shows epididymal

enlargement, scrotal skin thickening, and hydrocele. There is no effect on intratesticular blood flow. The disease is generally self-limited and responds to steroid therapy (*21*).

UNCOMMON ETIOLOGIES

More rare causes of acute scrotal pain and swelling include referred pain from retroperitoneal or intra-abdominal pathology including obstructing renal stones, psoas abscess, or perforated appendicitis (*16*). Intra-abdominal fluid or hemorrhage can track via a patent processes vaginalis causing a hydrocele or hematocele. Testicular tumors have also been reported as a cause of acute scrotal swelling (*12*). Meconium periorchitis is another uncommon cause of an acute scrotum in neonates (*22*).

CONCLUSION

Management of the acute scrotum should be timely and one should always consider testicular torsion in the differential. Color Doppler ultrasound is becoming the gold standard for diagnosis of acute scrotal pathology. In skilled hands it provides detailed anatomical and perfusion information that will aid in a definitive diagnosis. Based on clinical history, physical exam, and imaging, the surgeon has the final responsibility in assigning management for acute scrotal pathology.

REFERENCES

1. Schneck, Francis X., and Mark F. Bellinger. "Abnormalities of the Testes and Scrotum and their Surgical Management." *Campbell-Walsh Urology*. Eds. Andrew C. Novick, Alan J. Wein, Louis R. Kavoussi, Alan W. Partin and Craig A. Peters. 9th ed. Vol. 4. Philadelphia, PA: Saunders, 2006.
2. Rabinowitz, Ronald. "Evaluation of the Acute Scrotum." *Current Problems in Pediatric Urology*. Ed. Edmond T. Gonzales and David Roth. St. Louis, MO: Mosby, 1991. 333–39.
3. Mansbach, Jonathan M., Peter Forbes, and Craig Peters. "Testicular Torsion and Risk Factors for Orchiectomy." *Arch Pediatr Adolesc Med* 159 (2005): 1167–71.
4. Baker, Linda A., David Sigman, Ranjiv I. Mathews, Jane Benson, and Steven G. Docimo. "An Analysis of Clinical Outcomes Using Color Doppler Testicular Ultrasound for Testicular Torsion." *Pediatrics* 105 (2000): 604–7.
5. Liu, Chia-Chu, Shu-Pin Huang, Yii-Her Chou, Ching-Chia Li, Ming-Tsang Wu, Chun-Hsiung Huang, and Wen-Jeng Wu. "Clinical Presentation of Acute Scrotum in Young Males." *Kaohsiung J Med Sci* 23 (2007): 281–6.
6. Hulbert, William C., Ronald Rabinowitz, and Robert A. Mevorach. "Testicular Torsion." *Pediatric Clinical Advisor: Instant Diagnosis and Treatment*. Eds. Lynn C. Garfunkel, Jeffrey M. Kaczorowski and Cynthia Christy. 2nd ed. St. Louis, MO: Mosby, 2007. 554–5.
7. Sessions, Annette E., Ronald Rabinowitz, William C. Hulbert, Martin M. Goldstein, and Robert A. Mevorach. "Testicular Torsion: Direction, Degree, Duration and Disinformation." *The Journal of Urology* 169 (2003): 663–65.

8. Ringdahl, Erika, and Lynn Teague. "Testicular Torsion." *Am Fam Physician* 74 (2006): 1739–43.
9. Hulbert, William C., Robert A. Mevorach, and Ronald Rabinowitz. "Epididymitis." *Pediatric Clinical Advisor : Instant Diagnosis and Treatment*. Eds. Lynn C. Garfunkel, Jeffrey M. Kaczorowski and Cynthia Christy. 2nd ed. St. Louis, MO: Mosby, 2007. 191.
10. Bennett, Robert T., Bhagwant Gill, and Stanley J. Kogan. "Epididimytis in Children: The Circumcision Factor?" *J Urol* 160 (1998): 1842–4.
11. Davenport, Mark. "Acute Problems of the Scrotum." *BMJ* 312 (1996): 435–7.
12. Murphy, FL, H. Law, I. Mushtag, and NJ Sebire. "Testicular and paratesticular pathology in infants and children: the histopathological experience of a tertiary paediatric unit over a 17 year period." *Pediatr Surg Int* 23 (2007): 867–72.
13. Rakha, E., F. Puls, I. Saidul, and P. Furness. "Torsion of the testicular appendix: importance of associated acute inflammation." *J Clin Pathol* 59 (2006): 831–4.
14. Baldisserotto, Matteo, Joao Souza, Ana Pertence, and Marcelo Dora. "Color Doppler Sonography of Normal and Torsed Testicular Appendages in Children." *AJR* 184 (2005): 1287–92.
15. Deurdulian, Corinne, Carol A. Mittelstaedt, Wui K. Chong, and Julia R. Fielding. "US of Acute Scrotal Trauma: Optimal Technique, Imaging Findings, and Management." *RadioGraphics* 27 (2007): 357–69.
16. Kumar, Renu, J.K. Mahajan, and K.L.N. Rao. "Perforated appendix in hernial sac mimicking torsion of undescended testis in a neonate." *Journal of Pediatric Surgery* 43 (2008): E9–E10.
17. Hulbert, William. "Management of Torsion of the Testicle Recognized at Birth." *Current Problems in Pediatric Urology*. Ed. Edmond T. Gonzales and David Roth. St. Louis, MO: Mosby, 1991. 325–32.
18. Kaye, Jonathan D., Selwyn B. Levitt, Steven C. Friedman, Israel Franco, Jordan Gitlin, and Lane S. Palmer. "Neonatal Torsion: A 14-Year Experience and Proposed Algorithm for Management." *J Urol* 179 (2008): 2377–83.
19. Chiang, Ming-Chou, Hsiao-Wen Chen, Ren-Huei Fu, Reyin Lien, Ta-Min Wang, and Jen-Fu Hsu. "Clinical features of testicular torsion and epididymo-orchitis in infants younger than 3 months." *J Pediatr Surg* 42 (2007): 1574–7.
20. Yerkes, Elizabeth B., Frank M. Robertson, Jordan Gitlin, Martin Kaefer, Mark P. Cain, and Richard C. Rink. "Management of Perinatal Torsion: Today, Tomorrow or Never." *J Urol* 174 (2005): 1579–83.
21. Huang, Li-Hsin, Chun-Yan Yeung, Shyh-Dar Shyur, Hung-Chang Lee, Fu-Yuan Huang, and Nien-Lu Wang. "Diagnosis of Henoch-Schönlein purpura by sonography and radionuclear scanning in a child presenting with bilateral acute scrotum." *J Microbiol Immunol Infect* 37 (2004): 192–5.
22. Kalra, P., and J. Radhakrishnan. "Meconium Periorchitis." *Urology* 68 (2006): 202.

III Urinary Tract

13 Hydronephrosis: Prenatal and postnatal

Douglas E. Coplen

Abstract Renal pelvic dilation is the most common "abnormality" that is identified on prenatal ultrasonography. In the majority of cases detection does not alter the course of the pregnancy. A genitourinary abnormality is rarely apparent at birth. This chapter discusses the appropriate prenatal evaluation and consultation in fetuses with renal dilation. The subsequent postnatal evaluation and management of renal pelvic dilation and hydronephrosis is discussed in the last half of the chapter.

Keywords Hydronephrosis · Fetal renal dilation · Vesicoureteral reflux · UPJ obstruction · UVJ obstruction · Antenatal intervention

INTRODUCTION

Sonography was first used in 1964 to diagnose anencephaly. It is routinely used in obstetrical practices primarily related to high patient expectations and demand. The sensitivity of ultrasound widely varies depending upon the center performing the study and the anomaly. Ultrasound can identify major urologic abnormalities that may be apparent at birth (prune belly syndrome, bladder exstrophy, myelomeningocele) or can identify those that may not be clinically evident (i.e., renal pelvic dilation and hydronephrosis). When major abnormalities are identified, in utero intervention and pregnancy termination are options available early in pregnancy.

Historically the urologic conditions identified with fetal ultrasound presented with infection or pain. In the early 1980s pediatric urologists were presented with a new population of asymptomatic patients. There was an initial concern that an increased number of patients would undergo surgery but outcome data does not reveal an increased number of surgical procedures for these conditions in infants and children (*1*) over the last two decades.

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The most appropriate management and follow-up of these newborns with hydronephrosis continues to be debated.

There is only one randomized trial that evaluates the utility of prenatal sonography. The Routine Antenatal Diagnostic Imaging with Ultrasound trial (RADIUS) was performed in the late 1980s. Group 1 was randomized to ultrasounds early and late in pregnancy. The second group had ultrasounds only for medical indications. The fetal and maternal outcome was the same in both groups. The authors concluded that ultrasound screening for congenital abnormalities has no effect on perinatal outcome (*2*).

A real benefit of prenatal diagnosis is decreased infectious morbidity. Neonates with antenatally detected hydronephrosis are started on antibiotic prophylaxis at birth pending the post-natal radiographic evaluation. The subsequent incidence of infection in these children is very small (*3*). With the low incidence of infections, infant morbidity has decreased and the indications for surgical intervention have changed. Currently, pediatric urologists try to understand and predict the natural course of an anatomic abnormality in an asymptomatic patient. The indications for intervention in a newborn with posterior urethral valves are clear but the indications for intervention in a partially obstructed megaureter with 35% function are more debatable.

PRENATAL HYDRONEPHROSIS

Assessment of the fetal genitourinary tract is a part of every routine fetal ultrasound examination. If abnormalities are detected on the screening (dating) ultrasound then a detailed study specifically focusing upon amniotic fluid volume, renal size and parenchymal architecture, collecting system architecture, and bladder fullness and function is performed. By 16 weeks the volume of amniotic fluid is maintained by fetal urine production and remains constant throughout gestation. A filled bladder should always be visualized and functional emptying should be seen every 30–60 min. Most centers can now identify almost 100% of normal kidneys during a routine "dating" scan at 17–19 weeks. Markedly dilated collecting systems can be identified as early as 12–14 weeks (*4*).

Antenatal ultrasonographic detection of fetal genitourinary abnormalities was first reported in the 1970s. Bilateral renal agenesis, multicystic dysplastic kidney, infantile polycystic kidney disease, duplication anomalies, benign renal pelvic dilation, and hydroureteronephrosis are routinely identified. Fetal renal dilatation constitutes 50% of detected prenatal abnormalities.

The incidence of antenatally detected urinary tract dilatation can be as high as 1/100 but less than 20% of these may be clinically significant postnatally. A prospective study of 11,986 pregnancies scanned at 17 and 33 weeks revealed 33 abnormalities (3/1000). Only three of these were identified at 17 weeks (*5*). Scanning late in pregnancy yields a higher incidence of

Fig. 13.1. Fetal ultrasound showing isolated minimal renal pelvic dilation bilaterally.

sonographically evident collecting systems presumably because of a combination of delayed recanalization of the upper urinary tract and massive hypotonic urine output at that time Fig. 13.1. Fifty percent of cases detected after 28 weeks have post-natal imaging that is normal and only 1 in 1000 children with a normal antenatal study was found to have a significant urologic abnormality during 18 month follow-up (The majority of these were reflux) (*6*).

The anteroposterior diameter of the renal pelvis is the most reproducible measurement of RPD. The commonly accepted anteroposterior diameter cutoffs of RPD ≥4 mm at <33 weeks and ≥7 mm at >33 weeks for postnatal referral were described at our institution in 1991 with nearly 100% sensitivity but poor specificity for predicting postnatal obstruction (*7*). At times it is obvious that obstruction is very likely (See Fig. 13.2).

During prenatal counseling parents often want to know if their child will have normal renal function and whether or not surgery will be required. Ultrasound reveals nothing with respect to renal function although the sonographic detection of cortical cysts and echogenic parenchyma implies that dysplasia and severe renal damage are present. Fortunately the majority of detected dilation is unilateral and amniotic fluid is normal throughout pregnancy. In the absence of bilateral disease and in the presence of a normal contralateral kidney, nearly all of these children will have normal renal function. Survival for fetuses with unilateral renal obstruction is virtually 100%. In these cases no further evaluation or intervention is required during the prenatal period.

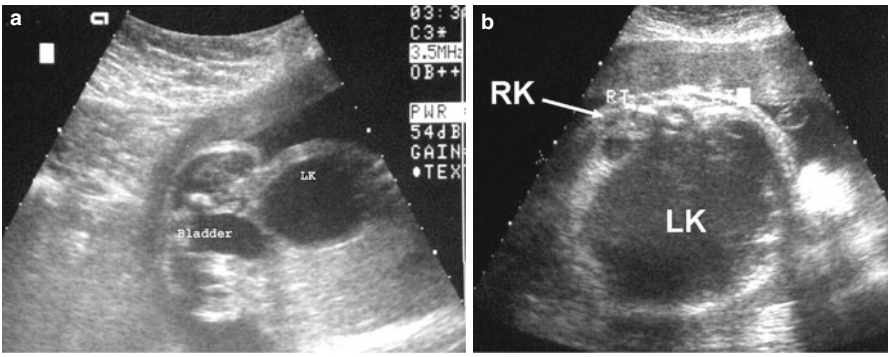

Fig. 13.2. Massive dilation of the left kidney that progressed during pregnancy. Renal pelvis was adjacent to bladder on a 28-week US (a) and filled the majority of the abdomen at 38 weeks gestation. This infant had significant respiratory distress at birth and required percutaneous drainage for extubation.

Prenatal Intervention

In fetuses with bilateral hydronephrosis the possibility of bladder outlet obstruction needs to be entertained (Fig. 13.3). Oligohydramnios is the best predictor of an adverse prognosis in this group and the timing of development may be the most important determinant of fetal outcome. Identification

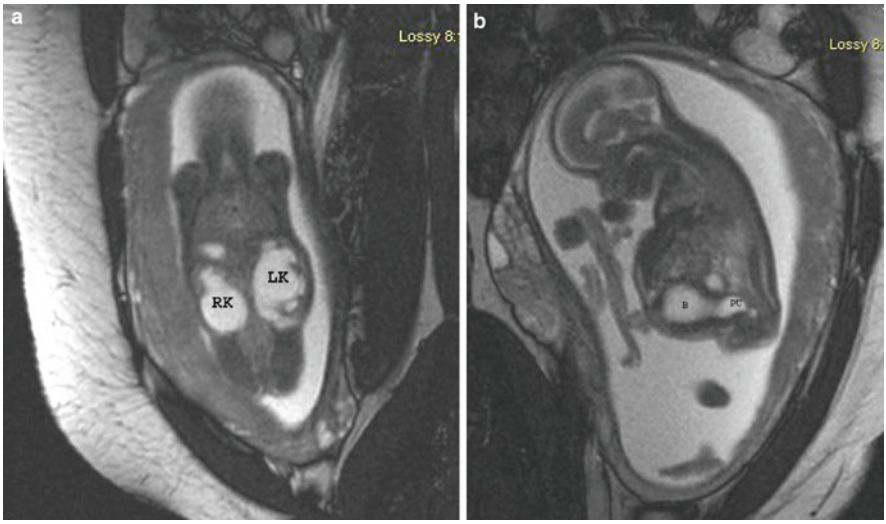

Fig. 13.3. (**a**) Fetal MRI showing marked bilateral hydroureteronephrosis. (**b**) A distended bladder (**b**) with a dilated prostatic urethra (PU) consistent with bladder outlet obstruction. Aminiotic fluid however is normal so there is no indication for prenatal intervention.

in the 3rd trimester has a far more favorable outcome than detection earlier in gestation.

There was a great deal of interest in fetal intervention for obstructive uropathy in the 1980s and 1990s. In utero intervention is thought to improve neonatal outcome by relieving obstruction (optimization of eventual renal function) and restoring normal levels of amniotic fluid (prevention of pulmonary hypoplasia). Hemorrhage, sepsis, abortion, premature labor (respiratory distress syndrome), and occurrence of renal dysplasia and pulmonary hypoplasia despite technically successful intervention are significant risks that must be weighed against potential benefits.

To avoid intervention in fetuses when not required or of no benefit, selection is a critical issue. Initial evaluation should begin with an in-depth ultrasound to confirm the diagnosis, the anatomic level of obstruction, the status of amniotic fluid, and the presence of associated anomalies (structural and/or chromosomal). If an associated life-threatening anomaly is present, the family should be counseled with respect to expectant management or termination of pregnancy. Fetal renal function needs to be evaluated by studying fetal urine electrolytes, urine protein and the rate of bladder filling after vesicocentesis (22-gauge needle). The healthy fetus makes hypotonic urine. With progressive renal damage, proximal tubular function is harmed and the urine becomes isotonic. Elevation in urinary sodium, chloride, and osmolality are indicative of renal injury and may represent irreversible dysplasia. In this case, the fetus is not a candidate for intervention. Intervention is potentially beneficial to only a very small percentage of fetuses with obstructive uropathy. Interventions should be focused early in gestation prior to the development of renal dysplasia.

Most series show little improvement in urologic outcomes after in utero urinary tract decompression (percutaneous vesicoamniotic shunt, open fetal surgery, or fetoscopic surgery) for obstructive uropathy and oligohydramnios (*8*). Children that survive after in utero intervention frequently have some degree of chronic renal insufficiency although their pulmonary function may be normal. They may also have significant orthopedic deformity related to prolonged oligohydramnios and this may seriously impact respiration.

Nonlethal conditions are best managed by early post-natal investigation and treatment, when indicated. If detection is late in gestation, the lungs can be tested for maturity and early delivery and post-natal decompression performed.

Both catheter placement and open fetal surgery carry significant fetal and maternal risks. Because there is great emotional pressure favoring intervention, the justification to date has been based upon experimental data and highly selected clinical anecdotes. Twenty-seven years after the first fetal intervention the most important question still remains whether or not prenatal surgical therapy can improve survival and reduce morbidity in affected fetuses/neonates.

POSTNATAL HYDRONEPHROSIS

As previously stated, the majority of urinary tract dilation is now detected by in utero ultrasound. In the absence of symptoms it may represent a transient physiologic condition, ongoing obstruction, or vesicoureteric reflux. Significant uropathy is present in one in 500 (*9*). A urologist must critically evaluate these findings to determine their clinical significance and whether intervention is required (Fig. 13.4). Less frequently, hydronephrosis is detected because of an abdominal mass, urinary tract infection, incontinence, or association with other anomalies (i.e., VACTERL syndrome (vertebral, anal, cardiac, tracheal, esophageal, renal, and limb)), or abnormalities seen during contrast or radionuclide radiography. In older children, vague, poorly localized, cyclic, or acute abdominal pain associated with nausea is common. Many of these children are initially seen by gastroenterologists. The cause for the intermittent obstruction is unclear, but renal function is almost always preserved. Hematuria after minor trauma or vigorous exercise may be a presenting feature, most likely secondary to rupture of mucosal vessels in the dilated collecting system (*10*). Episodic flank pain associated with diuresis is a common presenting feature in young adults but is uncommon in children.

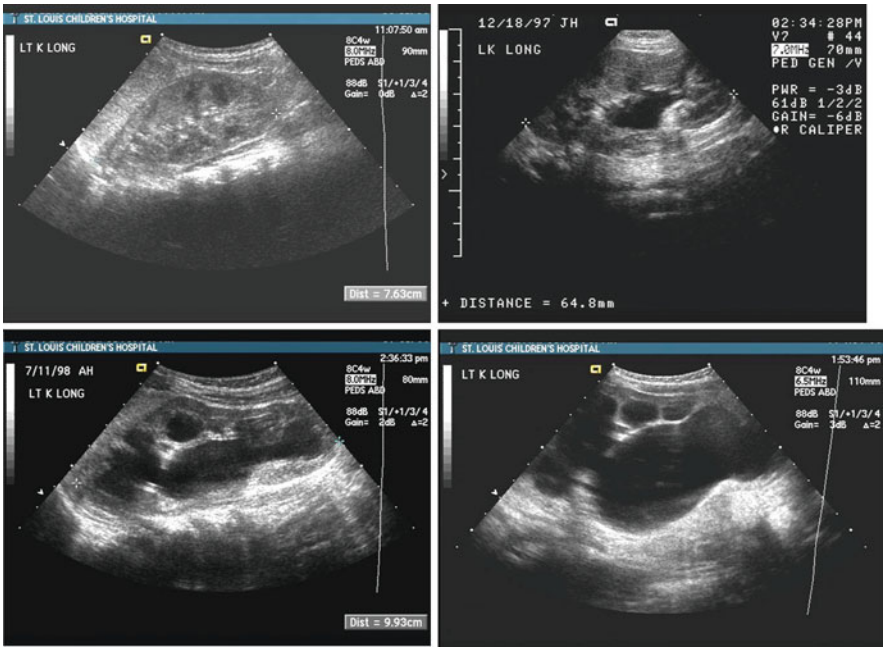

Fig. 13.4. Neonatal ultrasounds in neonates with prenatal renal dilation (RPD). (**a**) Essentially normal study showing a dark renal pyramid and no RPD. (**b**) Renal pelvic dilation with minimal caliectasis. (**c**) Diffuse caliectasis and mild cortical thinning. (**d**) Severe hydronephrosis with cortical thinning.

When an antenatal diagnosis of renal pelvic dilation or hydronephrosis is made, the initial postpartum evaluation is performed at 10–14 days of life to avoid false-negative studies resulting from transitional nephrology and underestimation of dilation that can be present in the first few days of life. The newborn is placed on preventive amoxicillin (20 mg/kg once a day), pending evaluation. Sonography confirms the presence of pelvic and calyceal dilation, with variable thinning of the renal parenchyma (Fig. 13.4). The presence of corticomedullary junctions on US is indicative of preserved function. US is used to evaluate the contralateral kidney, the bladder, and the distal ipsilateral ureter to avoid confusion with a ureterovesical junction obstruction (UVJ), but it will not provide functional information.

There has been extensive debate regarding the prenatal RPD threshold that triggers post-natal evaluation. This largely depends upon whether you are searching for obstruction and or reflux. Evaluation of renal pelvic dilation in conjunction with caliectasis and cortical thinning is well defined and usually includes a voiding cystourethrogram (VCUG) and a furosemide washout renal scan. Mild degrees of hydronephrosis are rarely indicative of significant urinary tract obstruction but may be indicative of vesicoureteral reflux. In general ultrasound is a poor predictor of reflux. As stated previously, early thresholds were directed at 100% sensitivity for obstruction. However, these resulted in lower RPD thresholds which give a very high false-positive rate. It is known that a post-natal evaluation may not be beneficial and is unnecessary in many infants.

Our recent series represents the largest prospective single center evaluation of RPD (*11*). The definition of pathology or uropathy is very important in the data interpretation. We chose to define renal obstruction as either a serial increase in hydronephrosis on postnatal sonography or declining function on renal scintigraphy. We specifically did not base this on renal drainage times because some infants had prolonged drainage times on renal scintigraphy ($T_{1/2}$>20 min) but dilation resolved with follow-up indicating that significant obstruction was not present. Using this definition we showed that a much larger RPD than is now commonly utilized more accurately discriminates between normal and obstructed kidneys. With long-term follow-up some smaller degrees of dilation may become symptomatic. This shows improved sensitivity and specificity for obstruction when a larger cut point is utilized. There is not an ideal threshold but a RPD of 15 mm, for example, accurately classifies the dilation (obstruction or benign dilation) 80% of the time (Fig. 13.5).

When suspicion for obstruction exists, the diuretic isotope renogram is the most widely used and most useful technique in the evaluation of hydronephrosis, differential renal function, and drainage of kidneys. The early uptake of the tracer indicates unilateral renal function, while the washout, augmented by the administration of a diuretic, is evaluated and plotted by a computer.

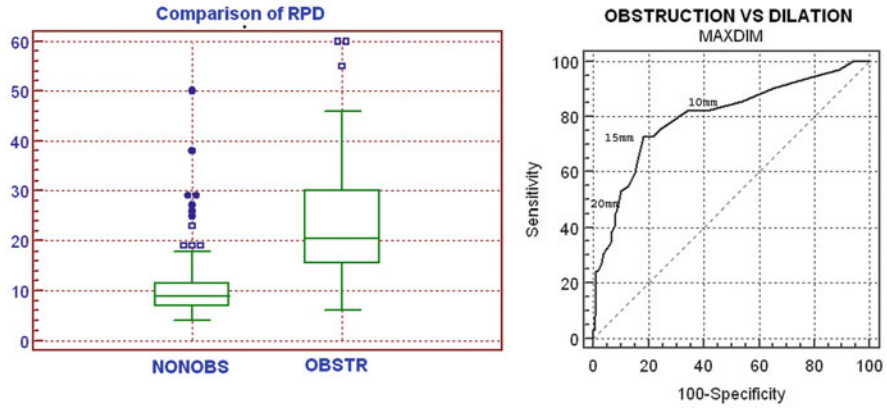

Fig. 13.5. (**a**) Graphic comparisons of maximum prenatal diameters between groups with obstructive hydronephrosis and benign renal dilation. A *box* has several lines – median, upper quartile, lower quartile, 1.5 times the interquartile range (IQR). The data points beyond 1.5 IQR are denoted by *filled squares*. **(b)**. The receiver operating characteristics curve characterizes the overall diagnostic accuracy of the maximum diameter for discriminating those infants with obstruction from those without obstruction. For example an RPD threshold of 15 mm discriminates obstruction in 80% of fetuses with a sensitivity of 73% and a specificity of 82%. 10 mm has a sensitivity of 82% and a specificity of 59% and 20 mm has a sensitivity of only 47% and a specificity of 91%.

The study is obtained with either technetium 99m-diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA), whose renal clearance is by glomerular filtration, or ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG3), whose clearance is predominantly via proximal tubular secretion. MAG3 is more efficiently excreted than ^{99m}Tc-DTPA and gives better images, particularly in patients with impaired renal function.

The technique for diuretic renography should be standardized (*12*). Patients should be hydrated intravenously (15 mL/kg) 15 min before injection of the radionuclide. An indwelling catheter maintains an empty bladder and monitors urine output. The diuretic (1 mg/kg furosemide) is not administered until the activity in the hydronephrotic kidney and renal pelvis peaks. The tracer activity is then monitored for an additional 30 min, and a quantitative analysis completed. Historically, persistence of more than 50% of the tracer in the renal pelvis 20 min after diuretic administration ($T_{1/2}$>20) is diagnostic of obstruction although the applicability of this cutoff in pediatric patients is widely debated. False-positive results may occur when the immature neonatal kidney fails to respond to diuretic, when the patient is dehydrated, when the bladder is distended, when dilating reflux is present, or when the pelvis is significantly dilated.

Magnetic resonance (MR) urography can be used at any age. T_2-weighted images are independent of renal function, and hydronephrosis is readily detected. The anatomic images are excellent, but a good US often gives

the same information. Enhanced MR with gadolinium can give information regarding differential function if one kidney is anatomically and functionally normal (*13*).

The excretory urogram has limited use in the newborn because the neonatal kidney does not concentrate contrast well enough to provide adequate visualization of obstructed kidneys. It also is subjective with respect to differential renal function and degree of obstruction. The test may be indicated when more information is required regarding preoperative pelvic anatomy or to define better the level of obstruction when it is not clear from other studies. In the child with intermittent flank pain, an IVP may be diagnostic when performed during an episode of pain (Fig. 13.6).

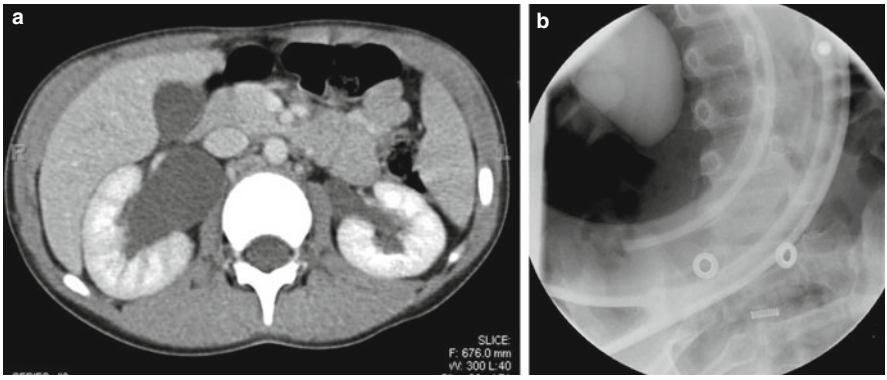

Fig. 13.6. Imaging in a male with a history of left prenatal dilation. The *left* dilation resolved by age 3 and the right kidney was always normal in appearance. (**a**) A noncontrast CT scan was obtained at age 5 when he was evaluated for severe right sided abdominal pain. A dilated renal pelvis is identified without urolithiasis. (**b**) IVP subsequently confirms a dilated renal pelvis and a kink at the junction of the ureter and the renal pelvis.

Indications for Surgical Intervention

When dilation or hydronephrosis is present, intermittent obstruction and pain is probably the most reliable indication for surgery. Recurrent infections are often a relative indication for intervention. There is no absolute or perfect definition of obstuction. Colic will almost always disappear after surgery. Diminished function, delayed drainage, progressions of dilation on US, and loss of renal function are all potential indicators of obstruction. Relying on the morphologic appearance of a dilated renal pelvis by using excretory urography or US is an insufficient basis on which to proceed with operation because many of these apparent abnormalities will completely resolve without surgical intervention (Fig. 13.7). The ongoing debate in the management of neonatal UPJ obstruction is the definition of significant obstruction (*6*). Diuretic renography has limitations in the neonate, although using the

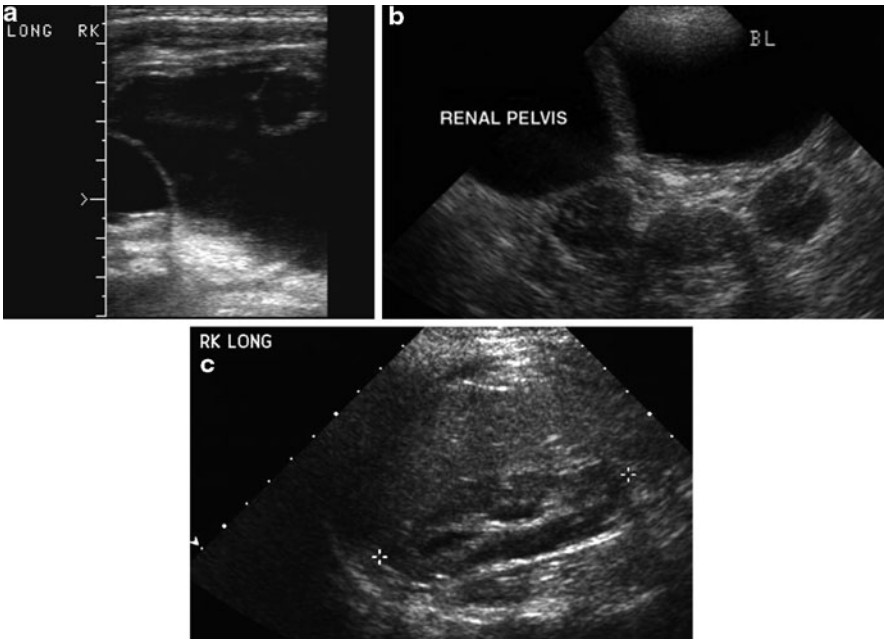

Fig. 13.7. Neonatal severe pyelocaliectasis. (**a**) Ultrasonography shows cortical thinning, calyectasis, and renal pelvic dilation consistent with UPJ obstruction. A Furosemide washout renal scan showed symmetric function. The $T_{1/2}$ on the right was prolonged and was calculated to be 81 min. On the basis of good renal function, observation was elected. (**c**) Follow-up sonogram 1 year later is normal. Renal scan at this time showed symmetrical function with normal washout (5 min).

"well-tempered" approach increases its value (*12*). The accumulation of the isotope in the dilated collecting system is quite variable, so that the timing of the diuretic can be premature or delayed. The standard $T_{1/2}$ cutoff of 20 min for obstruction in the neonate is misleading in many cases. Differential renal function or individual kidney uptake is the most useful information obtained during renography (*14*). An indication for operative treatment is diminished renal function in the presence of an obstructive pattern on renography. The cutoff point is arbitrary, but most centers believe that 35–40% function in the hydronephrotic kidney warrants surgical correction. However, one series of patients followed up because of dilated kidneys having no more than 25% total renal function were found to improve to more than 40% of total function in all cases without surgical treatment (*15*). Long-term studies of kidneys with greater than 40% function have shown that fewer than 15–20% will require surgical treatment for diminishing function, urinary tract infections, or unexplained abdominal pain. Some of these will regain some lost function.

The ultimate concern with an observational approach is that delaying surgical intervention until measurable deterioration of renal function

occurs is suboptimal. Randomization to surgical and observational arms is complicated by a difficult decision that a parent has to make for the asymptomatic child (*16*). Whether more emphasis should be placed on stasis and less emphasis on differential renal function is an unanswered question. Pyeloplasty can be safely performed in the infant. Early intervention eliminates the indefinite period of surveillance. The decision to follow up neonates nonoperatively requires vigilance and parental cooperation to avoid unnecessary complications.

If the child is first seen with acute pain or infection, it is advisable to wait 1–2 weeks to allow inflammation to resolve. Percutaneous drainage for sepsis is rarely required preoperatively. It should be strictly avoided in the absence of infection because of the inflammation that a tube in the renal pelvis induces.

Exploration of a poorly functioning kidney requires assessment of the renal parenchyma. If the parenchyma is grossly dysplastic or frozen-section analysis shows only dysplasia, then nephrectomy should be performed. No test accurately predicts recovery of function, so nephrectomy is rarely performed in the infant with UPJ obstruction.

Nonoperative management of the congenital UVJ obstruction is perhaps less controversial. Neonatal megaureter with obstruction suggested by renography but with preserved function can be safely observed. Most ureters will become radiographically normal with time(baskin). Surgical correction for decreasing function or recurrent infections is indicated in only 10–25% of patients in up to 7 years of follow-up. Evidence of delayed obstruction after normalization of radiographs has not been seen in these children.

Hydronephrosis and Reflux

Dilation or hydronephrosis may be indicative of reflux (incidence of 5–40%). Most studies show no significant correlation between the degree of postnatal dilation and the presence of reflux (*17*). Consequently most authors recommend a VCUG in all infants with a history of RPD. Parents are frequently reluctant to consent to a VCUG since the test is thought to be relatively invasive and uncomfortable for the child (*18*). Presumably the goal of reflux detection is the prevention of infections and renal scarring, but the clinical significance of this reflux is unclear in many cases. The majority is low grade and will spontaneously resolve (*19–20*). In the absence of infections, reflux is not associated with progressive renal injury. Most of the discussion in recent years has focused upon defining subpopulations that should have a VCUG.

We recently correlated pre- and postnatal US findings with reflux (*21*). Unlike the findings in the presence of obstruction there was no relationship between the magnitude of prenatal dilation and the presence of reflux. We did find that while post-natal ureteral dilation was not associated with a higher prevalence of reflux, caliectasis was a significant differentiator of

Table 13.1
Percentage of infants with vesicoureteral reflux related to prenatal and postnatal ultrasound findings

Ultrasound finding	*# infants*	*% reflux*	
No postnatal caliectasis	35	9%	$p<0.05$
Postnatal caliectasis	180	20%	
RPD < 10 mm and no caliectasis	22	5%	$p<0.02$
RPD < 10 mm and caliectasis	48	23%	
RPD ≥ 10 mm and no caliectasis	13	15%	
RPD ≥ 10 mm and caliectasis	132	25%	

reflux (Table 13.1). If a VCUG is not performed in the subgroup without caliectasis, the test could be avoided in 10–15% percent of the children (depending upon the prevalence in a given referral population). This approach would fail to diagnose low-grade reflux in only a small number of infants. Contrary to the recommendations of others this shows that isolated minimal pyelectasis is rarely associated with VUR and a tailored postnatal evaluation should be strongly considered in these infants (Fig. 13.8).

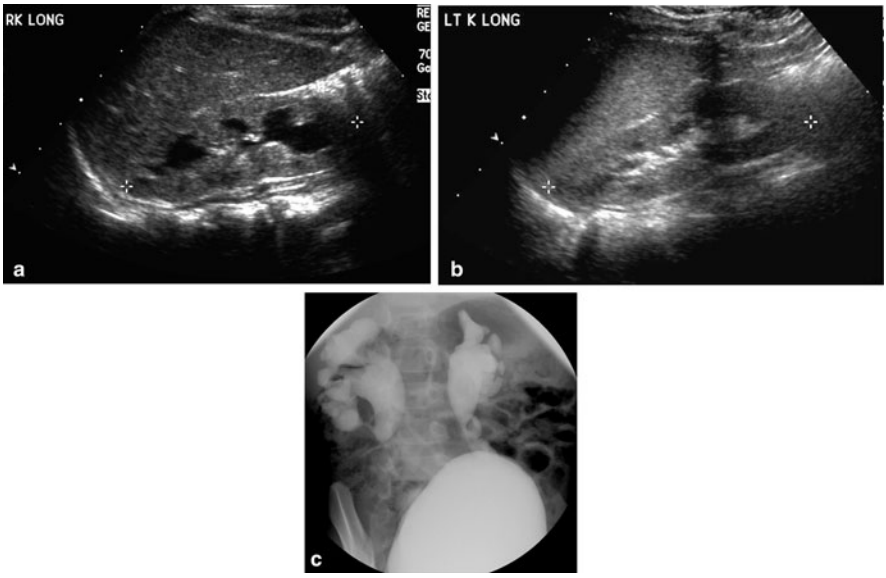

Fig. 13.8. Prenatal images showed 10–15 mm of renal pelvic dilation bilaterally. Postnatal images show minimal renal pelvic dilation but caliectasis is present (**a** and **b**). Bladder views were normal with no ureteral dilaton evident. A VCUG shows bilateral high grade reflux. This is indicative of the importance of caliectasis as well as the magnitude of RPD when determining the extent of postnatal imaging.

There is some clinical experience with a selective evaluation in infants with RPD. A recent prospective study followed infants with <10 mm postnatal pelvic dilation and no calyceal or ureteral dilation. Fifty-one newborns were managed conservatively without a VCUG and prospectively followed. There were no infections or sequelae over 2 years in infants on no antimicrobial prophylaxis (*22*). All children in the study had imaging at the end of the 2-year period and there were no adverse renal outcomes. In a retrospective evaluation, Yerkes et al. identified 16 infants with less than grade 2 dilation that were followed without a VCUG and none developed infections. Infants in this subset who were evaluated with a VCUG had a 15% incidence of low-grade reflux (*23*).

CONCLUSION

Renal pelvic dilation is commonly identified prenatally but rarely requires prenatal intervention, influences pregnancy outcome, or alters the site of delivery. Postnatal referral of the asymptomatic newborn is the most common reason for urologic evaluation. Because these infants have not had infections, pain or other signs and symptoms, determination of the significance of the dilation and the need for surgical correction is often difficult. The magnitude of prenatal dilation and postnatal caliectasis can help direct the evaluation.

REFERENCES

1. Capello SA, Kogan BA, Giorgi LJ, and Kaufman RP (2005) Prenatal ultrasound has led to earlier detection and repair of ureteropelvic junction obtruction. J Urol **174**, 1425–8.
2. Ewigman et al (1993) Effect of prenatal ultrasound screening on perinatal outcome. N Engl J Med **329**, 821–7.
3. Husmann DA, Ewalt DH Glenski WJ, et al (1995) Ureterocele associated with ureteral duplication and nonfunctioning upper pole segment: management by partial nephroureterectomy alone. J Urol **154**, 723–6.
4. Bronshtein M, Yotte JM, Brandes, JM, et al (1990) First and early second-trimester diagnosis of fetal urinary tract anomalies using transvaginal sonography. Prenat Diag **10**, 653–66.
5. Helin I, Persson P (1986) Prenatal diagnosis of urinary tract abnormalities by ultrasound. J Ped; **78**, 879–83.
6. Livera LN, Brookfield DSK, Egginton JA, et al (1989) Antenatal ultrasonography to detect fetal renal abnormalities: a prospective screening programme. Br Med J **298**, 1421–3.
7. Corteville JE, Gray DL, Crane JP (1991) Congenital hydronephrosis: correlation of fetal ultrasonographic findings with renal outcome. Am J Obstet Gynecol **165**, 384.
8. Freedman AL, Bukowski TP, Smith CA, Evans MI, Johnson MP, Gonzalez R (1996) Fetal Therapy for obstructive uropathy: specific outcome diagnosis. J Urol **156**, 720–4.
9. Dicke JM, Blanco VM, Yan Y, Coplen DE (2006) The type and frequency of fetal renal disorders and management of renal pelvis dilatation. J Ultrasound Med **25**, 973–7.
10. Carr MC, El-Ghoneimi A: Anomalies and surgery of the ureteropelvic junction in children. In Campbell-Walsh Urology, Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA (eds): 9th ed. Philadelphia, WB Saunders, 2007, p 3359.

11. Coplen DE, Austin PF, Yan Y, Blanco VM, and Dicke JM (2006) The magnitude of fetal renal pelvic dilatation can identify obstructive postnatal hydronephrosis, and direct postnatal evaluation and management. J Urol **176**, 724.
12. Conway JJ: "Well-tempered" diuresis renography: Its historical development, physiological and technical pitfalls and standardized technique protocol (1992). Semin Nucl Med **22**, 74.
13. McMann LP, Kirsch AJ, Scherz HC, Smith EA, et al (2006) Magnetic resonance urography in the evaluation of prenatally diagnosed hydronephrosis and renal dysgenesis. J Urol **176**, 1786–92.
14. Chung S, Majd M, Rushton HG, et al (1993) Diuretic renography in the evaluation of neonatal hydronephrosis: Is it reliable? J Urol **150**, 765.
15. Ulman I, Jayanthi VR, Koff SA (2000): The long-term followup of newborns with severe unilateral hydronephrosis initially treated nonoperatively. J Urol **164**, 1101.
16. Palmer LS, Maizels M, Cartwright PC, et al (1988) Surgery versus observation for managing obstructive grade 3 to 4 unilateral hydronephrosis: A report from the Society for Fetal Urology. J Urol **159**, 222.
17. Lee RS, Cendron M, Kinnamon DD and Nguyen HT (2006) Antenatal hydronephrosis as a predictor of postnatal outcome. A meta-analysis. Pediatrics **118**, 586.
18. Srivastava T, Betts G, Rosenberg AR, et al (2001) Perception of fear, distress and pain by parents of children undergoing a micturating cystourethrogram: A prospective study. J Paediatr Child Health **37**, 271.
19. Ismaili K, Avni FE, Wissing KM, and Hall M (2004) Long-term clinical outcome of infants with mild and moderate fetal pyelectasis: validation of neonatal ultrasound as a screening tool to detect significant nephrouropathies. J Pediatr **144**, 759.
20. Silva JMP, Oliveira EA, Diniz JSS, Bouzada MCF, Vergara RM, and Souza BC (2006) Clinical course of prenatally detected primary vesicoureteral reflux. Pediatr Nephrol **21**, 86.
21. Coplen DE, Austin PF, Yan Y, and Dicke JM (2008) Correlation of prenatal and postnatal ultrasound findings with the incidence of vesicoureteral reflux in children with fetal renal pelvic dilatation. J Urol **180**, 1631–4.
22. Kapadia H, Lidefelt K-J, Erasmie U, and Pilo C (2004) Antenatal renal pelvis dilatation emphasizing vesicoureteral reflux: two-year follow-up of minor postnatal dilatation. Acta Paediatr **93**, 336.
23. Yerkes, EB, Adams MC, Pope JC, and Brock JW (1999) Does every patient with prenatal hydronephrosis need voiding cystourethrography? J Urol **162**, 1218.

14 Vesicoureteral Reflux

Jeffrey S. Palmer and Christina B. Ching

Abstract Vesicoureteral reflux (VUR) is a common pediatric urologic condition. Several treatment modalities are available including observation and surgical intervention. The goal of surgical intervention is high success rate, minimal complications, and reduced length of hospitalization. Recent advances in surgery have resulted in outpatient open and cystoscopic surgery.

Keywords Vesicoureteral reflux · Urinary tract infection · etiology · Embryology · Cystography · Treatment · Extravesical reimplantation · Intravesical reimplantation · Laparoscopy · Endoscopic injection · Prophylactic antibiotics

OVERVIEW AND EPIDEMIOLOGY OF VESICOURETERAL REFLUX

Vesicoureteral reflux (VUR), one of the most common urologic abnormalities in children (*1*), is defined by the retrograde flow of urine from the bladder to the upper urinary tract (*2*, *3*). The incidence of VUR is 0.4–1.8% in the general pediatric population (*4*, *5*) and as high as 30–40% of children that presents with an acute urinary tract infection (UTI) (*1*, *6*). Since the natural history of reflux is to spontaneously resolve (60–80% natural resolution of grades I–III reflux), the true incidence is difficult to ascertain (*5*). The incidence of reflux initially found in newborn males is higher compared to females (6:1 ratio) (*7*), which is believed to be secondary to higher voiding pressures. However, with increasing age reflux is more common in females. A genetic predisposition, likely autosomal dominant in trait (*3*, *5*), is demonstrated by a 66% rate of reflux in the offspring of refluxing patients (*8*), approximately 32% of patient's siblings, and 100% of identical twins. There is some debate as to the utility of sibling screening of reflux given it is not the reflux itself, but rather its nephrologic consequences that are of concern; some suggest that it is better to screen a sibling with noninvasive tools to detect cortical abnormalities (such as with ultrasonography or nuclear renal

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scan) before screening for reflux itself in a so called "top-down approach" (*3*). African descent appears to protect against reflux with a tenfold decrease chance of reflux in those individuals (*9*).

It was in the 1950s that Hutch first noted the relationship between VUR and chronic pyelonephritis in a population of paraplegic patients (*10*). Hodson linked children with urinary tract infections (UTIs) and renal scarring to VUR (*11*). In 1979, Ransley and Risdon defined the pathophysiology of reflux nephropathy, tying together urinary infections, pyelonephritic scarring, and reflux (*12*).

ETIOLOGY OF REFLUX

VUR is categorized into primary and secondary reflux. Primary reflux refers to an abnormal ureterovesical junction (UVJ) while secondary reflux refers to an overwhelmed otherwise normal UVJ. Generally the ureter, bladder, and UVJ work together to prevent both types of reflux (Fig. 14.1). The normal peristaltic activity of the ureter alone should propagate urine in an antegrade direction (*13*) while the functional compliance of the bladder should keep intraluminal pressures low to prevent back pressure and reflux. Just as importantly, the anatomy of the UVJ itself, such as the intramural ureteral length, prevents the retrograde flow of urine. In primary VUR, the fundamental deficiency is in the UVJ anti-reflux anatomy or mechanism – usually the intramural tunnel length – while the bladder and ureters are normal. In contrast, secondary reflux is caused by bladder dysfunction (congenital, acquired, or behavioral) overwhelming an otherwise normal anti-refluxing UVJ. Examples of secondary reflux include posterior urethral valves, neurogenic bladder, and dysfunctional voiding, which may also involve constipation.

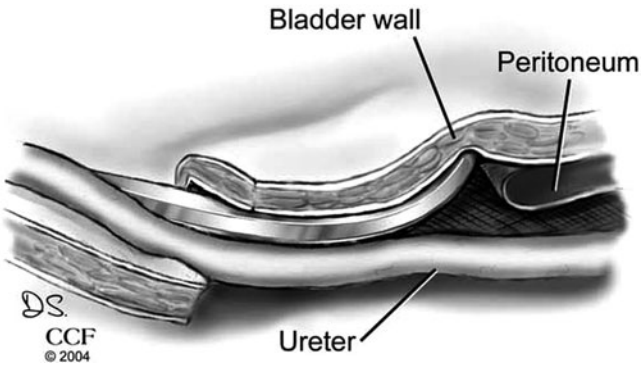

Fig. 14.1. Anatomy of the ureter, bladder, and ureterovesical junction working together to prevent vesicoureteral reflux. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2004–2010. All Rights Reserved.

EMBRYOLOGY

Primary reflux is thought to be caused by an anomaly during morphogenesis where a ureteral bud inserts high and lateral in the bladder wall (*3*). This is a result of the early budding of the ureter from the mesonephric or wolffian duct. The ureter is thus poorly incorporated into the bladder wall with a shorter than normal length of intravesical ureter (*4*). The more distant the site of origin of the bud from the wolffian duct, the more severe the degree of reflux. In contrast, if the ureteral bud is late in joining the bladder wall, the ureter inserts distally and medially resulting in what is known as an ectopic ureter. Normally, reflux is prevented by a simple flap valve-type mechanism reliant on the intravesical ureteral length. Bladder filling compresses the intravesical ureter against the bladder muscle, subsequently closing the intravesical portion of the ureter to prevent retrograde flow (*5*, *14*, *15*). Paquin described a 5:1 relationship between intravesical tunnel length and ureteral diameter necessary to prevent reflux. Given that the upper urinary tract and the ureteral bud develop as a unit, an early or late budding ureter may not properly stimulate a nephrogenic blastema, resulting in concomitant renal agenesis or dysplasia. In fact the finding of renal agenesis or a multicystic dysplastic kidney necessitates ruling out concomitant VUR (*3*, *5*).

PRESENTATION/SYMPTOMATOLOGY

The rational for treating reflux has been to prevent renal damage; however, the clinical spectrum of vesicoureteral reflux ranges from being asymptomatic and clinically silent to overt renal failure. Reflux itself is benign, but the reflux of infected urine is believed to be damaging to the renal system secondary to scarring. There is an association between reflux with urinary tract infections and renal scarring, with resulting decreased renal function, hypertension, and if severe enough, chronic kidney disease (*16*). Reflux nephropathy is one of the major causes of childhood hypertension and chronic renal failure (*1*, *2*). However, given that reflux can in fact be clinically silent and is only of clinical significance when associated with infection, there is some speculation that VUR could be a normal variant in the population of interest only in those predisposed to infection (*3*).

DIAGNOSIS

Given that reflux only poses a problem in a subset of patients with the finding, the real diagnostic dilemma is determining those with greatest risk of renal damage if reflux is found. Younger children are more sensitive to renal scarring from a single episode of pyelonephritis than older children with the greatest risk for post-infectious renal scarring occurring in

children less than 1 year old (*17*). It is suggested that children younger than 5 years old with an UTI, all children with a febrile UTI, and any male with a UTI regardless of age or fever be ruled out for VUR (*3*). The diagnosis of a urine culture proven UTI is necessary, as well as a thorough history and physical exam including circumcision status and method of urine collection.

The diagnosis of VUR is a radiographic diagnosis and cannot be made by routine cystoscopy. Voiding cystourethrogram (VCUG) requiring catheterization of the patient's bladder is the gold standard for diagnosis of VUR. Renal ultrasonography (RUS) can be used as a screening tool if the family or treating physician seeks a less aggressive method of evaluation with subsequent cystogram if renal abnormalities are identified. VCUG can be performed under fluoroscopy with an iodinated contrast, or it can be done with a radiopharmaceutical agent such as technetium Tc 99 pertechnetate. In the later, scintigraphic gamma cameras detect reflux. Such imaging has a much lower radiation exposure than that of fluoroscopy and greater sensitivity than the former, but the latter has poor anatomic detail (i.e., less specific grading of reflux and evaluation of bladder neck/urethra) (*3*, *18*).

Positioning instillation of contrast at the ureteral orifice (PIC technique) is a contemporary, controversial means of diagnosing reflux. It is designed for the subset of patients with recurrent febrile UTIs but normal VCUG. The theory is that these patients may have "occult" reflux that is not demonstrated on normal cystography (*19*). These patients may have patulous or laterally located orifices that are distendable during endoscopic evaluation allowing reflux (*20*). Tareen et al. demonstrated evidence of upper tract scarring/infection on imaging in 5 patients with a positive PIC even though their VCUG was negative (*21*). Hagerty et al. found that once patients with occult reflux were identified and treated, they had a significant reduction in incidence of febrile UTIs; thereby suggesting a high utility in PIC cystography (*20*). Overall, the stated sensitivity and specificity of a PIC cystogram is 100 and 87%, respectively (*19*).

There are few factors making the PIC technique controversial including the reported follow-up of approximately only a year. Another issue is the technique of performing the cystogram itself. For example, the instillation process itself could theoretically iatrogenically cause enough pressure to overwhelm an otherwise normal UVJ and cause reflux. Hagerty et al. refute this possibility by stating that elevating the contrast 1 m above the level of the bladder and allowing the gravity flow of contrast keeps intravesical pressures physiological (< 20 cm water) (*20*). Another consideration is that the finding of reflux on PIC cystogram may not change management given most patients with recurrent UTIs are placed on prophylactic antibiotics anyway. A beneficial feature of the PIC cystogram, however, is the possibility of a therapeutic endoscopic intervention at the time of a positive PIC cystogram (*20*, *21*).

GRADING

There are five grades of reflux as defined by the International Reflux Study Committee (*22*). The grade describes the involvement of the ureter, renal pelvis, and calyces on cystogram imaging of refluxing radiographic contrast. The grade of primary reflux is an important determinant in predicting spontaneous resolution of reflux (*3*).

Grade I: reflux into nondilated ureter
Grade II: reflux into the pelvis and calyces without dilatation
Grade III: mild to moderate dilatation of the ureter, renal pelvis, and calyces with minimal blunting of the fornices
Grade IV: moderate ureteral tortuosity and dilatation of the pelvis and calyces
Grade V: gross dilatation of the ureter, pelvis, and calyces, loss of papillary impressions, and severe ureteral tortuosity

OTHER UROLOGIC CONSIDERATIONS WITH VUR

An ureteropelvic junction obstruction (UPJO) is another very common pediatric urologic diagnosis and can be found concurrently in a pediatric patient with reflux. It is more common, however, for reflux to be found in association with a UPJO (11%) compared to UPJO found in association with reflux (0.75%) (*23*). Secondary UPJO may be a result of high grade reflux kinking the upper ureter or creating ureteral inflammation and thus a functional UPJO. If both VUR and the UPJO are deemed necessary for surgical correction, the UPJO is usually corrected first to eliminate possible worsening transient obstruction as a reimplant heals (*23*). VUR can also be found in the case of ureteral duplication, associated with the lower pole moiety secondary to a more lateral and proximal insertion of its ureter.

PREGNACY AND VUR

The potential for future pregnancies must be taken into account in young girls with reflux. Bacteriuria increases during pregnancy secondary to decreased bladder tone from edema and hyperemia. There is also physiologic dilatation of the upper collecting system that can potentiate the slow transit of urine and thus bacterial growth (*3*). Women with a history of VUR do have a higher incidence of UTI during pregnancy than those without reflux (38 versus 6%), regardless of whether their VUR was ever corrected (*24*). Otherwise VUR itself has minimal impact on any morbidity associated with pregnancy. What has been shown to have significant impact on pregnant females is the presence or absence of renal scarring. Once again, it is not the reflux itself, but its sequelae that results in morbidity. Renal scarring has been associated with an even higher incidence of UTI than patients with VUR and a higher incidence of hypertension (in first pregnancies), preeclampsia, and low birth weight (*24*).

TREATMENT OPTIONS

Spontaneous resolution of reflux depends on initial grade and age of diagnosis, and unilateral versus bilateral condition. For example, the younger age of diagnosis and the lower initial grade of reflux have a higher chance of spontaneously resolution compared the older child and higher grade of reflux. Also, the child with unilateral compared to bilateral grade 3 reflux has a greater chance of spontaneous resolution. The physician should have a discussion with the parents on all of the treatment options discussing both the published and personal success rates with the different options. This explanation is important since the management of reflux can result in a great deal of anxiety for parents.

Management of vesicoureteral reflux consists of three main options: (*1*) antibiotic prophylaxis, (*2*) open/laparoscopic surgery, and (*3*) cystoscopic injection. These categories can be subdivided into specific treatment modalities based on surgical technique and material used for cystoscopic injection with an ever continuing effort to improve outcome, decrease morbidity, and enhance efficiency. Again, it must be stressed that dysfunctional voiding must be identified and appropriately addressed first and treated before being able to adequately address VUR either medically or surgically. This principle also applies to the treatment of constipation and neurologic etiologies. When a child with a sacral dimple or tuft of hair, for example, is identified, a neurologic cause should be determined.

MEDICAL MANAGEMENT – PROPHYLACTIC ANTIBIOTICS

The optimal management of VUR is controversial, but antibiotic suppression has long been a primary tool of management used (*25*). The reasoning behind the use of antibiotic suppression is based on the observation that VUR may spontaneously resolve with time (*2*) and that renal damage is due to infection rather than reflux itself (*5*). As a result, the goal is the prevention of UTIs until VUR resolves. Amoxicillin in children younger than 2 months of age and trimethoprim-sulfamethoxazole and nitrofurantoin in children older than 2 months are commonly used antibiotics for suppression. Dosing is administered at nighttime given that is the time of longest physiologic retention of urine (*3*, *18*). It has been shown 51% of VUR can resolve without renal scarring simply on prophylactic antibiotics (*26*); this efficacy, however, is dependent on patient compliance. In a study by Hensle et al., they found only 17% of patients were compliant with therapy with a mean patient compliance of 41.4% (*27*). One of the potential complications of long-term antibiotic use is the development of antibiotic resistance with resulting breakthrough infections. There is also the risk of side effects such as nausea, vomiting, abdominal pain, and bone marrow suppression (*2*, *28*). The 2006 International Reflux Study compared surgery or antibiotic prophylaxis in 252 children treated for VUR. After 10 years of follow-up, they

found no overall difference between treatment modalities in new renal scarring, renal growth function, DMSA scan, or GFR. There was a significantly higher frequency of pyelonephritis in the medical group ($p < 0.03$), however. Their recommendations were to base treatment on anticipated patient compliance, available local expertise, and family preference (*6*).

OPEN SURGICAL TREATMENT

Since the development of open surgical correction for primary VUR in the 1950s, it has been considered the gold standard of treatment (*29*). The cure rate for open surgery regardless of technique is between 95 and 100% (*4*, *30*, *31*).

Indications for surgical intervention include unsuccessful medical management and breakthrough infections on antibiotic prophylaxis (*2*, *16*, *32*), persistent high grade reflux (IV–V) (*2*, *5*, *33*), persisting or worsening VUR (*32*), and/or significant or progressing renal scarring (*33*, *34*). Some relative indications include patients in whom antibiotic compliance may be an issue (*34*), complex anatomy such as a large hutch diverticulum, and/or in patients with persisting VUR after 1–2 endoscopic interventions (*4*, *35*).

The main principle of surgical correction is to fulfill the Paquin 5:1 ratio of ureteral length to ureteral diameter with appropriate elongation of the intravesical submucosal ureteral tunnel (*14*, *15*), permitting only the unidirectional antegrade flow of urine (*4*, *36*). Detrusor muscle may be used to over-sew the tunnel for further support contributing to the anti-reflux, valve-like effect (*3*). Successful anti-reflux surgery includes (*1*) preservation of renal function; (*2*) recreation of a competent ureteral tunnel; and (*3*) elimination of recurrent UTI (*37*).

Types of Surgery

The basic steps of reimplantation are (*1*) ureterolysis, (*2*) creation of a new ureteral tunnel, (*3*) ureteral advancement, and (*4*) anastomosis of ureter with bladder. The anastomosis between the ureter and bladder can be done in continuity known as a nondismembered repair or with the ureter disconnected from the bladder in what is called a dismembered repair (*38*). Close attention to the direction of entry of the submucosal tunnel into the bladder is necessary in order to prevent ureteral kinking, angulation, or stenosis.

These steps can be completed intravesically, extravesically, or a combination of both. The techniques differ by how the ureter is approached and whether one opens the bladder for ureteral reimplantation or not. There are various benefits and complications related to each technique described with continual effort to try decrease morbidity and increase efficacy.

Intravesical Ureteral Reimplantation

In intravesical ureteral reimplantation, the bladder is opened in order to mobilize the ureter, create a longer submucosal tunnel, or for the actual reimplantation technique. It can be used as part of the surgical approach or for the entirety of the operation. Postoperative catheter drainage is usually performed for an appropriate period of time to ensure adequate healing.

One of the most common intravesical reimplantation techniques is the Cohen cross-trigonal reimplant (*39*) (Fig. 14.2). This technique consists of directing a tunnel across the trigone toward the contralateral bladder wall in order to lengthen the submucosal distance. The ureters follow the normal curve of the bladder decreasing the risk of ureteral kinking with subsequent obstruction. In bilateral reimplantation, the ureters end up on opposing bladder walls, each in their own separate tunnel to prevent adhesions. This procedure is well suited for small, thick walled bladders and is ideal when used in conjunction with bladder neck reconstruction given the superior displacement of the ureters. As an added overall benefit, there is virtually no risk of passing through bowel or broad ligament as is possible with the Politano-Leadbetter approach (*40*). Given these factors as well as a success rate of up to 99% (*31*), it has been historically a popular treatment option. Its main disadvantage is the alteration in anatomy making later retrograde catheterization difficult for radiographic studies, stent insertion, and management of nephrolithiasis. In a study evaluating minimally invasive treatment for upper tract nephrolithiasis in patients with previous cross-trigonal

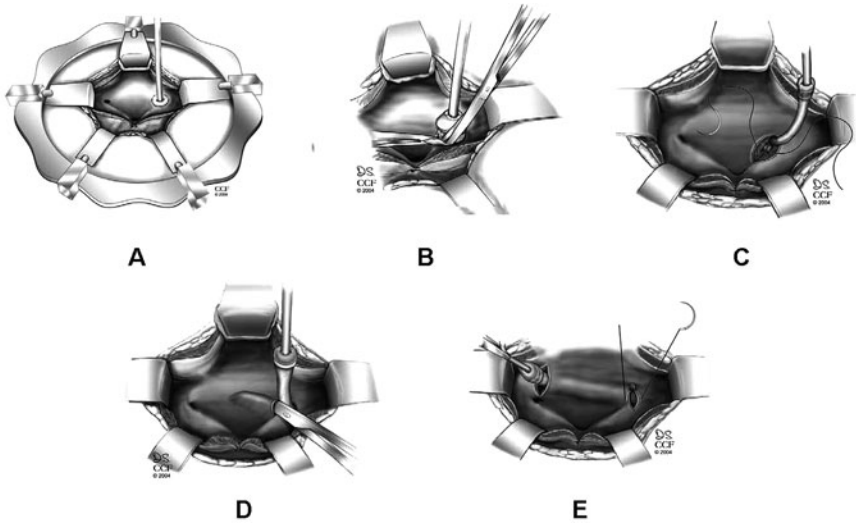

Fig. 14.2. Cohen cross-trigonal ureteral reimplantation. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2004–2010. All Rights Reserved.

reimplantation, they found these patients required more invasive intervention for their nephrolithiasis as compared to those patients whose reimplantation was not cross-trigonal. Ureteral access after a cross-trigonal technique can be challenging.

Another technique is the Politano-Leadbetter, initially described in 1958 (Fig. 14.3). In this technique, the native ureter is brought through a new hiatus superior to its old one, elongating the submucosal tunnel. The technique is actually a combination of an intravesical and extravesical approach: the ureter is initially mobilized intravesically but then passed extravesically before being brought back inside the bladder through its new hiatus. Ultimately, while the ureter enters the bladder superior and medial to the original orifice, it is in normal anatomic position, enabling later ureteroscopic manipulation if necessary. The major risk of the procedure is entering the peritoneum and injuring bowel given the blind extravesical portion of the surgery. The procedure is contraindicated in megaureters or if the patient is past puberty in age (*30*).

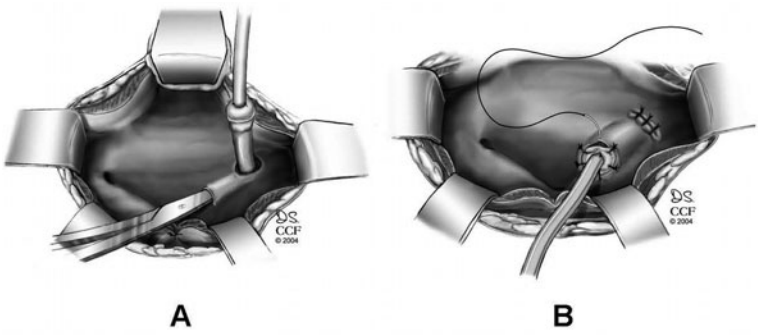

Fig. 14.3. Politano-Leadbetter ureteral reimplantation. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2004–2010. All Rights Reserved.

The Glenn-Anderson technique is another intravesical modality (*41*) (Fig. 14.4). Success rates have been reported as high as 98% with this repair. In this technique, a longer submucosal tunnel is created by advancing the ureter distally and medially toward the bladder neck through its original hiatus. This technique is simplistic and rapidly executable. The visibility of the terminal ureteral segments is excellent with minimal dissection or trauma to the paravesical space. Given the ureters are advanced to a physiologic position in the trigone, the risk of angulation or kinking is decreased (*36*). The one drawback is that tunnel length is limited by the distance from the original hiatus to the bladder neck. There has been a modification described, however, where a large hiatus is intentionally developed to permit at least another 6–8 cm of distal mobilization (*36*).

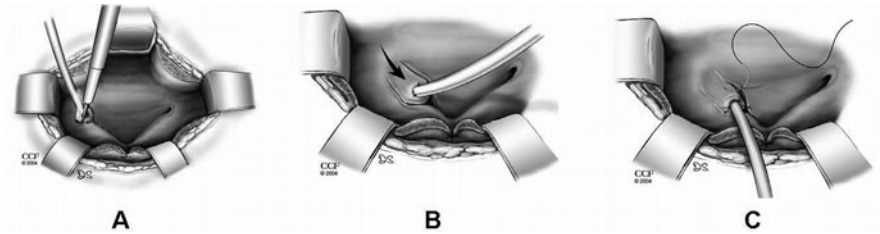

Fig. 14.4. Glenn-Anderson ureteral reimplantation. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2004–2010. All Rights Reserved.

Extravesical Ureteral Reimplantation

Lich and Gregoir separately described an extravesical repair for VUR in 1961 and 1964, respectively (*42*, *43*). In this technique, there is no penetration of the bladder mucosa; the juxtavesical ureter is isolated and a submucosal bed for the ureter is created by incising the detrusor superiorly and laterally to the ureteral hiatus. The detrusor is then sutured over the ureter. Of note, this method of reimplantation is widely used in renal transplantation. In a modification by Zaontz of what has now become known as the Lich-Gregoir repair, the ureteral orifice is advanced after making the extravesical incision in the detrusor muscle to further lengthen the submucosal tunnel (*44*).

The extravesical approach affords several advantages over the intravesical techniques. Given the bladder mucosa is not entered, there is no postoperative hematuria and less reported bladder spasms. Ureteral stenting is unnecessary unless there is simultaneous tapering of the ureter as part of the repair/reconstruction (Fig. 14.5). Success rates have been quoted near if not comparable to intravesical repairs, ranging from 94% as originally described by Lich in 37 patients to as high as 97.7% in a series of 429 ureters (*37*, *44*). Akin to these findings of decreased hematuria and pain, as well, as earlier time to discharge, recent investigations have looked into performing extravesical reimplants on an outpatient basis. An outpatient reimplantation reduces the risk of hospital-acquired infections and potentially reduces the psychological trauma of hospitalization on children (*45*, *46*, *47*). The most recent studies to evaluate the plausibility of outpatient ureteral reimplantation have been done by Palmer (*48*, *49*, *50*) (Fig. 14.6). He reports the success of using a family-centered care, along with critical pathway, and modified operative technique in performing extravesical repairs on an outpatient basis. In one of his more recent study, he evaluated 60 children (51 girls and 9 boys) between 0.9 and 10.5 years of age (mean of 5.1 years) who underwent extravesical reimplant. Twenty-four unilateral and 36 bilateral procedures were performed. Fifty-four children (90%) were able to be discharged home the same day; the other six children (10%) went home the following day. All of the patients who underwent a unilateral procedure were

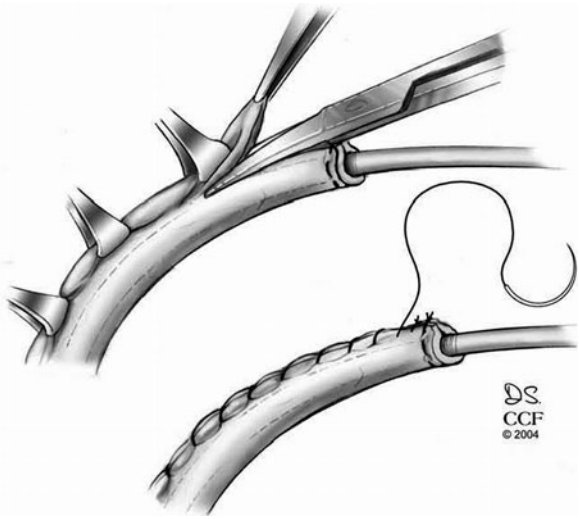

Fig. 14.5. Ureteral tapering for dilated ureter. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2004–2010. All Rights Reserved.

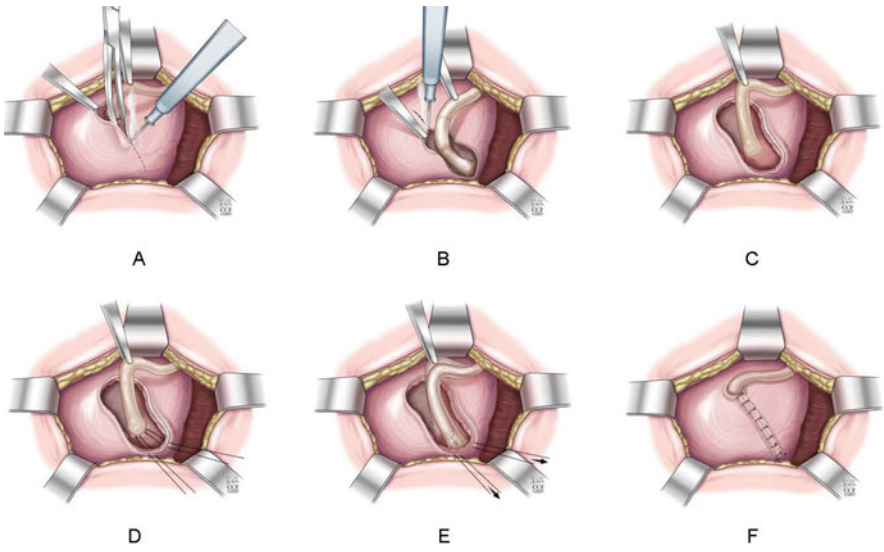

Fig. 14.6. Extravesical ureteral reimplantation with Palmer modification. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2004–2010. All Rights Reserved.

able to be discharged the same day, while 83% of the bilateral procedures were discharged same day. When evaluating the last 40 consecutive patients (14 unilateral and 26 bilateral), all patients were discharged home the same

day of surgery within 5 h after surgery. This was able to be done without increased morbidity or the need for additional analgesics. None of the children required hospitalization after discharge, experienced urinary retention, or were diagnosed with an acute urinary tract infection (*48*).

Historically, extravesical reimplantation has been reserved for unilateral reflux given the risk of transient urinary retention following bilateral reimplantation (*49*). This has been the main criticism of this technique and has been thought secondary to injury of small branches of the pelvic plexus (*51*). It has been reported that approximately 15–20% of patients undergoing bilateral reimplantation have temporary voiding dysfunction (*52*). The nerves involved in this process have been localized to the medial aspect of the ureter traveling outside the mesoureter (*51*). They subsequently form a network around the ureter just outside Waldeyer's sheath at the ureterovesical junction, continuing in the detrusor muscle distal and lateral to the ureter upon entry into the bladder (*53*). Transection, suturing, excessive electrocautery, or simply neuropraxia from tissue handling can result in nerve injury causing unilateral or bilateral detrusor impairment (*54*). By limiting dissection to between the mesoureter and ureteral adventitia, prudent electrocautery, restricting the detrusor incision distal to the UVJ, and gently handling the tissue injury can be avoided. In a study that limited dissection to the lateral ureterovesical attachments, the incidence of acute urinary retention was decreased to 2% (*55*).

McAchran and Palmer specifically evaluated their experience with bilateral reimplants in 50 toilet-trained patients with even more encouraging results on voiding dysfunction. They reported no cases of acute urinary retention for their series (*54*). As their surgical technique, they performed a Zaontz modification of the Lich-Gregoir repair, limiting ureteral dissection, ureteral mobilization, and detrusor dissection to as distally as possible. They specifically minimized surrounding dissection and preserved the obliterated umbilical artery to avoid damage to the afferent nerve fibers arising in proximity to the obliterated umbilical artery. They established a critical pathway for preoperative, intraoperative, and postoperative management of the patient that they believed was an integral factor in their success. The pathway includes extensive parental and patient education and a strict postoperative regimen of aggressive ambulation and timed voiding. This was in effort to prevent bladder overdistention, decreased bladder contractility, diminished awareness of bladder sensation, and decreased micturition reflex activity. In their study, all patients were able to be discharged the day following surgery. In follow-up, all patients were cured of reflux on voiding cystourethrogram.

Most recently, Palmer updated his experience with bilateral extravesical repair, including further refinement of his critical pathway and surgical technique. He included 84 toilet-trained children (64 girls and 20 boys) between 1.9 and 12.8 years of age (mean of 4.6 years) all undergoing bilateral extravesical reimplants. The initial 78 patients (93%) were discharged on postoperative day number one; however, the most recent six patients were discharged

on the same day as surgery. All patients voided spontaneously postoperative without any instances of urinary retention. There were no cases of acute urinary tract infections and no patients required rehospitalization. On postoperative voiding cystourethrogram, all patients had radiographic resolution of their vesicoureteral reflux (*50*).

Extravesical reimplantation can be used as an effective salvage therapy. In a study evaluating feasibility of performing extravesical reimplantation after failed endoscopic injection, there were no reported intraoperative complications for the 30 patients undergoing extravesical reimplantation after dextranomer/hyaluronic acid failure (*56*). All but two patients were discharged home within 24 h postoperatively; prolonged bladder drainage was not necessarily after the surgery. The only noticeable intraoperative finding was that bleb migration occasionally resulted in a smaller caliber ureter for reimplantation.

LAPAROSCOPIC TECHNIQUES

While open surgery has been highly successful in treating VUR, interest has continued regarding other techniques that might improve the current standard of success while reducing patient morbidity and medical cost. There is also social pressure to find minimally invasive techniques of treating VUR (*34*). Given the rise in popularity in laparoscopy for many modalities of surgery, it has also been investigated as an alternative, "less invasive" procedure to open VUR surgery with the goal of decreased postoperative bladder spasms and faster catheter removal, reduced incisional pain, and improved cosmesis (*32*). Studies have shown that the main limiting factor for length of hospitalization has been the presence of a bladder catheter, not pain control (*35*), emphasizing the importance of this parameter.

Laparoscopic reimplantation (either extravesical or intravesical) using the same principles as the previously described open surgeries have been reported (*4*). Both the Cohen cross-trigonal and the Gil-Vernet meatal advancement repairs have been described laparoscopically. In the Gil-Vernet procedure, the mucosa of the trigone is incised vertically and both ureters are reapproximated to the midline with a single submucosal suture. Unfortunately, however, his has only been met with a roughly 60% success rate (*57*).

Laparoscopic Transvesical Reimplantation

Laparoscopic transvesical reimplantation approach applied the open techniques laparoscopically (*58*, *59*, *60*). During intravesical repair, the laparoscopic ports are initially placed transvesically with subsequent insufflation of the bladder (*4*). Glycine irrigation was initially reported to distend the bladder (*59*); however, subsequently the bladder has been insufflated with carbon dioxide, yielding a 96% success rate after laparoscopic Cohen

cross-trigonal ureteral reimplantation (*60*). Kutokov et al. looked at their experience using vesicoscopic cross-trigonal reimplantation for VUR or Glenn Anderson repair for primary obstructing megaureter in 32 patients (*32*). In the reflux arm, the observed postoperative success rate was 92.6% while being 80% in the primary obstructing megaureter arm. The authors noted that dissection of the intramural ureter and intravesical suturing were the most challenging parts of the operation; visibility was obscured given the limited intravesical space combined with effluxing urine and bleeding from the detrusorotomy. They reported a 12.5% incidence of postoperative urine leak – either at former port sites or at the neoureterovesical anastomosis. Their incidence of ureteral stricture at neoureterovesical anastomosis was 6.3%. They found that children < 2 years old and bladders < 130 milliliters in volume were at risk for higher complications, likely due to the technical complexity of this procedure in an already restricted space.

Laparoscopic Extravesical Reimplantation

Extravesical reimplants have also been performed laparoscopically with various challenges specific to this repair. Even extravesically, exposure is limited and is particular to trying to locate and dissect out the ureter. Create the extravesical tunnel without injuring the urothelium has also been noted to be of difficulty. Again, the laparoscopic technique takes longer than the open technique (*3*, *4*). one study found it took a mean of 1.75 h for unilateral and 3.75 h for bilateral laparoscopic Lich-Gregoir reimplants as compared to 30 min and 1 h for open Lich-Gregoir (*61*).

CYSTOSCOPIC INJECTION

Cystoscopic injection is another minimally invasive technique. Matouschek first described endoscopy intervention in 1981 (*62*) and it was clinically popularized by O'Donnell and Puri (*63*). In this technique, a submucosal injection of material is made at the refluxing ureteral orifice to bolster the intravesical portion of ureter. This leads to coaptation of the distal ureter and thus prevents reflux (*5*, *64*). The procedure itself can be quite short (performed in as quickly as 15 min), requiring a short anesthetic, and is associated with minimal postoperative care. The postoperative narcotic pain control is minimal and overall hospital stay needs only be 2–3 h (*1*, *41*). It is an easily repeated technique if necessary, as well. Unfortunately, its main limitation is that its overall efficacy is less than that of open surgery and there is questionable long-term safety information available (*41*). Success rates with endoscopic injection only approach those of open surgery after two or more injections (*32*); even then, there is concern for long-term durability of this procedure with long-term failure rates quoted anywhere between 17 and 91% (*33*).

Endoscopic management has been compared to surgical intervention for VUR in a meta-analysis by Elder et al. In their analysis, they reviewed 63 articles of 5526 patients with 8101 renal units. They found decreasing rates of success of a single endoscopic treatment for increasing grade of reflux, regardless of the type of injection material used: 78.5% for grade I/II, 72% for grade III, 63% for grade IV, and 51% for grade V. When more than one endoscopic procedure was performed, the aggregate success rate rose only to 85–87%; conversely, open surgical correction results in success rates of 96% for children with grades I–IV reflux as reported by the AUA guidelines (*18*). As a result, Elder et al. concluded reflux resolution was favorable with endoscopic management, however, was not as successful as definitive open surgical correction and may in fact required two or three procedures (*25*).

Yu et al. reported an 82.2% success in patients after one endoscopic injection that rose to 90.7% when repeated in a second injection (*28*). In a study that looked at success of a single injection in patients with both unilateral and bilateral reflux, they found an overall success rate of 82.3% in 195 patients treated with polydimethylsiloxane (*65*). Given endoscopy can be easily repeated, the efficacy of increasing number of injections has been investigated (*66*). In patients who failed initial endoscopic treatment, a 90% cure rate was found upon second injection. Of four patients with persistent VUR after a second injection in this study, one resolved after a third injection, one failed a third injection, and two opted for a different intervention option. Similarly, only a 34% success rate after a third endoscopic injection has been quoted in another meta-analysis by Elder (*23*), suggesting a low yield with more than two endoscopic treatments and encouraging consideration of an alternative treatment at that point (*66*).

Importantly, variables predicting success of endoscopic treatment have been sought to enable appropriate patient selection. It is well established that failure rate of endoscopic treatment increases with increasing grade of reflux (*1*). In a multivariate analysis, greater physician experience, lower preoperative grade reflux, and lack of previous injection therapy significantly improved success of endoscopic intervention ($p < 0.05$) (*67*). Generally, early failure of endoscopic treatment or persistence of reflux is considered a technical failure, secondary to misplacement of the injection material or technical difficulties. The injection may be too deep to cause appropriate coaptation or may migrate out of place along Waldeyer's sheath. Technical difficulties may arise due to anatomical anomalies such as a complex duplex system, a neurogenic bladder, or failed previous bladder surgery. Late failure or recurrence of reflux has in the past been attributed to the type of material used for injection (unstable or biodegradable). More recently, however, bleb migration has been thought to play an important role. This phenomenon, seen more frequently in unstable bladders and children >3 years of age, may be due to micturition itself and/or high bladder pressures displacing the material medially and distally (*68*).

Injection Material

The type of material used in endoscopic treatment has been of considerable interest. A variety of materials have reportedly been used: including polytetrafluoroethylene paste (PTFE, Teflon), dextranomer/hyaluronic acid (Deflux®), polydimethylsiloxane (PDS), bovine collagen, chondrocytes, fat, and even autologous blood (*5*, *25*, *34*). The ideal characteristics of an injection material include inert in nature, low in cost, easy to inject but viscous enough to create a compact bolus, result in minimal tissue reaction, and be noncarcinogenic (*25*, *64*, *69*). The material should be stable with low risk for migration, absorption, or reduction in size once injected (*25*, *69*). PTFE has been found in one comparison study to be most effective with a 63% cure rate in comparison to dextranomer/hyaluronic acid and collagen which were 53 and 56%, respectively (*69*). In a study looking at 1–4 injections of PTFE, they found a success rate of 95% (*70*). This success has been demonstrated to be sustained for up to 11–17 years of follow-up in another study (*71*). While widely used in Europe, PTFE has never gained FDA approval in the USA due to reports of particle migration to other organ systems such as regional lymph nodes, the central nervous system, and lungs. Given roughly 90% of the particles are <40 μm in size, there is the potential for direct injection of the particles into capillaries and their subsequent embolization (*25*, *34*, *64*).

Some other agents investigated include cross linked bovine collagen. It does not appear, however, to have good durability over time and raises the possibility of an immunogenic response (*5*, *34*, *64*). Autologous injectable materials such as blood, fat, chondrocytes, and bladder muscle cells have also proven ineffective given their risk for biodegradation and contraction (i.e., only 8% efficacy with autologous blood (*69*)). The only FDA-approved agent in the USA, currently, is dextranomer/hyaluronic acid (Dx/HA, aka Deflux®). Approved in October 2001, dextranomer is biodegradable, nonallergenic, nonmutagenic, with no immunogenic properties. Dx/HA therapy has shown only a slight decrease in volume of <20% over time. It has not been associated with embolization or far migration (*25*, *66*). Its overall success with first injection has been quoted at roughly 69% (*34*).

CONCLUSION

VUR can be a threat to renal health in some patients, but may also pose simply a passing phase in the developing child's anatomy. Those children requiring surgical intervention have several surgical modalities that can be utilized. Open ureteral reimplantation is the gold standard for surgical correction of VUR. With the aid of good techniques both in and out of the operating room, ureteral reimplantation may routinely become an outpatient procedure, as described by Palmer (*48*, *50*, *54*). Minimally invasive options such as laparoscopic and cystoscopic techniques continue to be developed to determine their future in surgical management of VUR.

REFERENCES

1. Puri, P., Pirker, M., Mohanan, N., et al. (2006) Subureteral dextranomer/hyaluronic acid injection as first line treatment in the management of high grade vesicoureteral reflux. *J Urol* **176**, 1856–1860.
2. Oberson, C., Boubaker, A., Ramseyer, P., et al. (2007) Endoscopic and surgical treatment of vesico-ureteral reflux in children. *Swiss Med Wkly* **137**, 471–475.
3. Khoury, A., Bagli, D.J. (2007) Reflux and Megaureter. In: *Campbell-Walsh Urology 9th Edition* (**Vol. 4**). Wein, A.J., Kavoussi, L.R., Novick, A.C., Partin, A.W., Peters, C.A. (Ed.), Saunders Elsevier, Philadelphia, PA, 3423–3467.
4. Capozza, N., Caione, P. (2007) Vesicoureteral reflux: surgical and endoscopic treatment. *Pediatr Nephrol* **22**, 1261–1265.
5. Belman, A.B. (1997) Vesicoureteral reflux. *Ped Clin of North Am* **44**(5), 1171–1190.
6. Jodal, U., Smellie, J.M., Lax, H., et al. (2006) Ten-year results of randomized treatment of children with severe vesicoureteral reflux. Final report of the International Reflux Study in Children. *Pediatr Nephrol* **21**, 785–792.
7. Marra, G., Barbieri, G., Dell-Agnola, C.A., et al. (1994) Congenital renal damage associated with primary vesicoureteral reflux detected prenataly in male infants. *J Pediatr* **124**, 726–730.
8. Noe, H.N., Wyatt, R.J., Peeden , J.N. Jr., et al. (1992) The transmission of vesicoureteral reflux from parent to child. *J Urol* **148**, 1869–1871.
9. Chand, D.H., Rhoades, T., Pie, S.A., et al. (2003) Incidence and severity of vesicoureteral reflux in children related to age, gender, race and diagnosis. *J Urol* **170**, 1548–1550.
10. Hutch, J.A. (1952) Vesicoureteral reflux in the paraplegic: Cause and correction. *J Urol* **68**, 457.
11. Hodson, C.J. (1959) The radiologic diagnosis of pyelonephritis. *Proc R Soc Med* **52**, 669.
12. Ransley, P.G., Risdon, R.A. (1979) The pathogenesis of reflux nephropathy. *Contrib Nephrol* **16**, 90–97.
13. Weiss, R.M. (2007) Physiology and pharmacology of the renal pelvis and ureter. In: *Campbell-Walsh Urology 9th Edition* **(Vol. 4**). Wein, A.J., Kavoussi, L.R., Novick, A.C., Partin, A.W., Peters, C.A. (Ed.), Saunders Elsevier, Philadelphia, PA, 1891–1921.
14. Paquin, A.J. Jr., Zinner, N.R., Arbuckle, L.D. (1964) Mechanical factors influencing the demonstrability of vesicoureteral reflux. *Am J Surg* **107**, 492–496.
15. Paquin, A.J. (1964) Considerations for the management of some complex problems for ureterovesical anastomosis. *Surg Gynecol Obstet* **118**, 75–92.
16. Faust, W.C., Pohl, H.G. (2007) Role of prophylaxis in vesicoureteral reflux. *Curr Opin Urol* **17**, 252–256.
17. Winberg, J. (1992) Commentary: Progressive renal damage from infection with or without reflux. *J Urol* **148**, 1733–1734.
18. Elder, J.S., Peters, C.A., Arant, B.S. Jr., Ewalt, D.H., Hawtrey, C.E., Hurwitz, R.S., Parrott, T.S., Snyder, H.M. 3rd, Weiss, R.A., Woolf, S.H., Hasselblad, V. (1997) Pediatric vesicoureteral reflux guidelines panel summary report on the management of primary vesicoureteral reflux in children. *J Urol* **157**(5), 1846–1851.
19. Rubenstein, J.N., Maizels, M., Kim, S.C., Houston, J.T.B. (2003) The PIC cystogram: a novel approach to identify "occult" vesicoureteral reflux in children with febrile urinary tract infections. *J Urol* **169**, 2339–2343.
20. Hagerty, J.A., Maizels, M., Cheng, E.Y. (2008) The PIC cystogram: Its place in the treatment Algorithm of Recurrent Febrile UTIs. *Adv Urol* **763620**.
21. Tareen, B.U., Bui, D., McMahon, D.R., Nasrallah, P.F. (2006) Role of positional instillation of contrast cystography in the algorithm for evaluating children with confirmed pyelonephritis. *Urology* **67**(5), 1055–1057.
22. Duckett, J.W., Bellinger, M.F. (1982) A plea for standardized grading of vesicoureteral reflux. *Eur Urol* **8**, 74–77.
23. Lebowitz, R.L, Blickman, J.G. (1983) The coexistence of ureteropelvic junction obstruction and reflux. *AJR Am J Roentgenol* **140**, 231–238.

24. Hollowell, J.G. (2008) Outcome of pregnancy in women with a history of vesico-ureteric reflux. *BJUI* **102**, 780–784.
25. Elder, J.S., Diaz, M., Caldamone, A.A., et al. (2006) Endoscopic therapy for vesicoureteral reflux: a meta-analysis I. Reflux resolution and urinary tract infection. *J Urol* **175**, 716–722.
26. King, L.R., Kazmi, S.O., Belman, A.B. (1974) Natural history of vesicoureteral reflux. Outcome of a trial of nonoperative therapy. *Urol Clin North Am* **1**, 441.
27. Hensle, T.W., Hyun, G., Grogg, A.L., et al. (2007) Part 2: examining pediatric vesicoureteral reflux: a real-world evaluation of treatment patterns and outcomes. *Curr Med Res Opin* **23 supp 4**, S7–13.
28. Yu, R.N., Roth, D.R. (2006) Treatment of vesicoureteral reflux using endoscopic injection of nonanimal stabilized hyaluronic acid/dextranomer gel: initial experience in pediatric patients by a single surgeon. *Pediatrics* **118**, 698–703.
29. Schwentner, C., Oswald, J., Lunacek, A., et al. (2006) Lich-Gregoir reimplantation causes less discomfort than Politano-Leadbetter technique: results of a prospective, randomized, pain scale-oriented study in a pediatric population. *Eur Urol* **49**, 388–395.
30. Steffens, J., Stark, E., Haben, B., et al. (2006) Politano-Leadbetter ureteric reimplantation. *BJU Int* **98**, 695–712.
31. Glassberg, K.I., Laungani, G., Wasnick, R.J., et al. (1985) Transverse ureteral advancement technique of ureteroneocystotomy (Cohen reimplant) and a modification for difficult cases (experience with 121 ureters). *J Urol* **134**, 304–307.
32. Kutikov, A., Guzzo, T.J., Canter, D.J., et al. (2006) Initial experience with laparoscopic transvesical ureteral reimplantation at the Children's Hospital of Philadelphia. *J Urol* **176**, 2222–2226.
33. Simforoosh, N., Nadjafi-Semnani, M., Saeed, S. (2007) Extraperitoneal laparoscopic trigonoplasty for treatment of vesicoureteral reflux: novel technique duplicating its open counterpart. *J Urol* **177**, 321–324.
34. Ogan, K., Pohl, H.G., Carlson, D., et al. (2001) Parental preferences in the management of vesicoureteral reflux. *J Urol* **166**, 240–243.
35. Canon, S.J., Jayanthi, V.R., Patel, A.S. (2007) Vesicoscopic cross-trigonal ureteral reimplantation: a minimally invasive option for repair of vesicoureteral reflux. *J Urol* **178**, 269–273.
36. Glenn, J.F., Anderson, E.E. (1978) Technical considerations in distal tunnel ureteral reimplantation. *J Urol* **119**, 194–198.
37. McDougall, E.M., Urban, D.A., Kerbl, K., et al. (1995) Laparoscopic repair of vesicoureteral reflux utilizing the Lich-Gregoir technique in the pig model. *J Urol* **153**(2), 497–500.
38. Houle, A.M., McLorie, G.A., Heritz, D.M., et al. (1992) Extravesical nondismembered ureteroplasty with detrusorrhaphy: a renewed technique to correct vesicoureteral reflux in children. *J Urol* **148**, 704–707.
39. Cohen, S.J. (1975) Ureterozystoneostomie. Eine neue antirefluxtechnik. *Aktuelle Urologic* **6**, 1–8.
40. Politano, V.A., Leadbetter, W.F. (1958) An operative technique for the correction of vesicoureteral reflux. *J Urol* **79**, 932–941.
41. Gonzales, E.T., Glenn, J.F., Anderson, E.E. (1972) Results of distal tunnel ureteral reimplantation. *J Urol* **107**, 572–575.
42. Gregoir W (1964) The surgical treatment of congenital vesico-ureteral reflux. *Acta Chir Belg* **63**, 431–439.
43. Lich, R. Jr., Howerton, L.W. Jr., Goode, L.S., Davis, L.A. (1964) The ureterovesical junction of the newborn. *J Urol* **92**, 436–438.
44. Zaontz, M.R., Maizels, M., Sugar, E.C., et al. (1987) Detrusorrhaphy: extravesical ureteral advancement to correct vesicoureteral reflux in children. *J Urol* **138**, 947–949.
45. Putman, S., Wicher, C., Wayment, R., Harrell, B., Devries, C., Snow, B., Cartwright, P. (2005) Unilateral extravesical ureteral reimplantation in children performed on an outpatient basis. *J Urol* **174**(5), 1987–1989.

46. Marotte, J.B., Smith, D.P. (2001) Extravesical ureteral reimplantation for the correction of primary reflux can be done as outpatient procedures. *J Urol* **165**, 2228–2231.
47. Putman, S., Wicher, C., Wayment, R., et al. (2005) Unilateral extravesical ureteral reimplantation in children performed on an outpatient basis. *J Urol* **174**, 1987–1990.
48. Palmer, J.S. (2008) Extravesical ureteral reimplantation: an outpatient procedure. *J Uro* **180**, 1828–1831.
49. Headman, P., Palmer, J.S. (2009) A critical pathway for successful outpatient ureteral reimplantation: a nursing perspective. *J Perianesthesia Nurs* **24(3)**, 163–166.
50. Palmer, J.S. (2009) Bilateral extravesical ureteral reimplantation in toilet-trained children: a short-stay procedure without urinary retention. *Urology* **73(2)**, 285–288.
51. Leissner, J., Allhoff, E.P., Wolff, W., et al. (2001) The pelvic plexus and antireflux surgery: topographical findings and clinical consequences. *J Urol* **165**, 1652–1655.
52. Barrieras, D., Lapointe, S., Reddy, P.P., et al. (1999) Urinary retention after bilateral extravesical ureteral reimplantation: does dissection distal to the ureteral orifice have a role? *J Urol* **162**, 1197–1200.
53. Yucel, S., Baskin, L.S. (2003) Neuroanatomy of the ureterovesical junction: clinical implications. *J Urol* **170**, 945–948.
54. McAchran, S.E., Palmer, J.S. (2005) Bilateral extravesical ureteral reimplantation in toilet trained children: is 1-day hospitalization without urinary retention possible? *J Urol* **174**, 1991–1993.
55. David, S., Kelly, C., Poppas, D.P. (2004) Nerve sparing extravesical repair of bilateral vesicoureteral reflux: description of technique and evaluation of urinary retention. *J Urol* **172**, 1617–1620.
56. Elmore, J.M., Kirsch, A.J., Perez-Brayfield, M.R., et al. (2006) Salvage extravesical ureteral reimplantation after failed endoscopic surgery for vesicoureteral reflux. *J Urol* **176**, 1158–1160.
57. Okamura, K., Kato, N., Tsuji, Y., et al. (1999) A comparative study of endoscopic trigonoplasty for vesicoureteral reflux in children and adults. *Int J Urol* **6**, 562–566.
58. Peters, C.A., Woo R (2005) Intravesical robotically assisted bilateral ureteral reimplantation. *J Endourol* **19**, 618–621.
59. Gill, I.S., Ponsky, L.E., Desai, M., et al. (2001) Laparoscopic cross-trigonal Cohen ureteroneocystostomy: novel technique. *J Urol* **166**, 1811.
60. Yeung, C.K., Sihoe, J.D.Y., Borzi, P.A. (2005) Endoscopic cross-trigonal ureteral reimplantation under carbon dioxide bladder insufflation: a novel technique. *J Endo* **19**(3), 295–299.
61. Shu, T., Cisek, L.J., Moore, R.G. (2004) Laparoscopic extravesical reimplantation for postpubertal vesicoureteral reflux. *J Endourol* **18**, 441–446.
62. Matouschek, E. (1981) New concept for the treatment of vesico-ureteral reflux. Endoscopic application of teflon. *Arch Esp Urol* **34**, 385.
63. O'Donnell, B., Puri, P. (1984) Treatment of vesicoureteric reflux by endoscopic injection of teflon. *Br Med J (Clin Res Ed)* **298**, 7.
64. Kirsch, A.J., Perez-Brayfield, M.R., Scherz, H.C. (2003) Minimally invasive treatment of vesicoureteral reflux with endoscopic injection of dextranomer/hyaluronic acid copolymer: the Children's Hospitals of Atlanta experience. *J Urol* **170**, 211–215.
65. Van Capelle, J.W., De Haan, T., El Sayed, W., et al. (2004) The long-term outcome of the endoscopic subureteric implantation of polydimethylsiloxane for treating vesicoureteric reflux in children: a retrospective analysis of the first 195 consecutive patients in two European centres. *BJU Int* **94**, 1348–1351.
66. Elmore, J.M., Scherz, H.C., Kirsch, A.J. (2006) Dextranomer/hyaluronic acid for vesicoureteral reflux: success rates after initial treatment failure. *J Urol* **175**, 712–715.
67. Lorenzo, A.J., Pipp Salle, J.L., Barroso, U., et al. (2006) What are the most powerful determinants of endoscopic vesicoureteral reflux correction? Multivariate analysis of a single institution experience during 6 years. *J Urol* **176**, 1851–1855.
68. Capozza, N., Caione, P., De Gennaro, M., et al. (1995) Endoscopic treatment of vesicoureteric reflux and urinary incontinence: technical problems in the paediatric patient. *BJU* **75**, 538–542.

69. Sugiyama, T., Hanai, T., Hashimoto, K., et al. (2004) Long-term outcome of the endoscopic correction of vesico-ureteric reflux: a comparison of injected substances. *BJU Int* **94**, 381–383.
70. Puri, P., Ninan, G.K., Surana, R. (1995) Subureteric Teflon injection (STING). Results of an European study. *Eur Urol* **27**, 71–75.
71. Chertin, B., Colhoun, E., Velayudham, M., et al. (2002) Endoscopic treatment of vesicoureteral reflux: 11 to 17 years of follow-up. *J Urol* **167**, 1443–1445.

15 Urinary Tract Obstruction

Wolfgang H. Cerwinka and Andrew J. Kirsch

Abstract Congenital urinary tract obstruction is distinct from obstruction in the mature kidney in as much as it induces various degrees of renal dysplasia and hypoplasia. The vast majority of prenatally detected uropathies does not require fetal interventions because of acceptable postnatal renal function and unacceptably high fetal morbidity and mortality secondary to the procedure. Symptoms vary depending on age of diagnosis and include urinary tract infection, urosepsis, failure to thrive, pain, nausea, hematuria, and hypertension. The underlying principle for the determination of obstruction by imaging studies is delayed excretion of contrast agents/tracers in a dilated urinary system. The availability of only two treatment options for urinary tract obstruction, observation or surgery, has created a great deal of controversy when to intervene. Indications for surgery are greatly individualized and depend on a multitude of clinical variables including the urologist's experience and parental preference. This chapter discusses the etiology, epidemiology, presentation, diagnosis, and treatment of the most common and some rare entities of urinary tract obstruction in children.

Keywords Hydronephrosis · Urinary tract obstruction · Ureteropelvic junction · Ureterovesical junction · Posterior urethral valves

Abbreviations and Acronyms

US	Ultrasound
IVP	Intravenous pyelography
VUR	Vesicoureteral reflux
UTI	Urinary tract infection
ESRD	End stage renal disease
UPJ	Ureteropelvic junction
VCUG	Voiding cystourethrography
MAG-3	Mercaptoacetyltriglycine

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DTPA	Diethylenetriaminepentaacetic acid
DRF	Differential renal function
T1/2	Half time excretion of radiotracer
MRU	Magnetic resonance urography
RTT	Renal transit time
RPG	Retrograde pyelogram
IVC	Inferior vena cava
CT	Computed tomography
MRI	Magnetic resonance imaging
UVJ	Ureterovesical junction
PUV	Posterior urethral valves
AUV	Anterior urethral valves

INTRODUCTION

Urinary tract obstruction is defined as any condition restricting urinary flow that already has or will impair renal function or renal function development. Urinary tract obstruction presents with collecting system dilation proximal to the level of obstruction and is seen on imaging studies as hydronephrosis. Congenital urinary tract obstruction is distinct from obstruction in the mature kidney. Obstruction in the developing kidney induces various degrees of renal dysplasia and hypoplasia and causes rising creatinine (glomerular injury), acidosis (tubular injury), and nephrogenic diabetes insipidus (collecting duct injury); all or one of these abnormalities may be present. Renal dysfunction may be progressive if the urinary tract obstruction remains uncorrected and even with a previously corrected obstructing lesion that has inflicted renal damage. Renal obstruction is the largest single cause of renal failure and comprises 23% of all indications for transplantation (*1*). With the increasing usage of ultrasound (US) screening during pregnancy, most congenital obstructive uropathies are diagnosed prenatally and a rising number of patients are referred to the pediatric urologist for prenatal counseling. The vast majority of prenatally detected uropathies, however, does not require fetal interventions because of acceptable postnatal renal function and unacceptable high fetal morbidity and mortality secondary to the procedure. Consequently, prenatal counseling focuses on parental education and reassurance as well as on outlining a postnatal plan of management. Table 15.1 lists indications for fetal intervention and Table 15.2 summarizes the work-up of prenatal hydronephrosis. Most cases of urinary tract obstruction that are discovered before birth will not produce clinical manifestations. Symptoms vary depending on age of diagnosis and include urinary tract infection, urosepsis, failure to thrive, pain, nausea, hematuria, and hypertension. The availability of only two treatment options for urinary tract obstruction, observation or surgery, has created a great deal of controversy when to intervene. Indications for surgery are greatly

Table 15.1
Indications for fetal intervention

XY karyotype
Absence of major congenital malformations
Bilateral hydronephrosis
Distended bladder
Dilated posterior urethra
Oligohydramnios
Favorable fetal urinary indices
Singleton pregnancy
Non-cystic kidney

Table 15.2
Postnatal management of prenatal hydronephrosis

Postnatal management	*Indications*
Antibiotic prophylaxis	All cases except mild hydronephrosis
Ultrasound	Bilateral prenatal hydronephrosis of any degree Unilateral renal pelvis AP diameter >10 mm in third trimester
VCUG	Hydronephrosis on postnatal ultrasound or All cases of prenatal hydronephrosis
MAG-3 scan	Severe unilateral or bilateral hydronephrosis

individualized and depend on a multitude of clinical variables including the urologist's experience and parental preference.

HYDROCALYCOSIS

Hydrocalycosis is defined as a cystic dilation of a major calyx and is very rare. It is caused by either an extrinsic obstruction such as a parapelvic cyst or vessel or by stenosis (infection, trauma) or without obvious cause. The calyceal dilation is usually mild and asymptomatic with the most common symptom being flank pain; however, urinary stasis can lead to infection, stones, or hematuria. Differentiation of hydrocalycosis from caliectasis secondary to ureteral obstruction, large calyceal diverticulum, and megacalycosis is essential and made by intravenous pyelography (IVP). A dismembered infundibulopyelostomy is indicated in cases of vascular obstruction whereas infundibular stenosis is treated by intubated infundibulotomy or partial nephrectomy. Percutaneous approaches are preferred because of their low associated morbidity.

INFUNDIBULOPELVIC DYSGENESIS

Infundibulopelvic dysgenesis is caused by stenosis of one or more infundibula with or without the renal pelvis. Congenital obstruction is the underlying reason for cystic dysplasia, a focal form of multicystic dysplastic kidney. Infundibulopelvic dysgenesis is usually found bilaterally and is frequently associated with vesicoureteral reflux (VUR). Patients usually present with urinary tract infection (UTI), hypertension, or flank pain. Prognosis is poor secondary to significant unilateral renal damage or end stage renal disease (ESRD) in all patients with bilateral involvement.

URETEROPELVIC JUNCTION OBSTRUCTION

Epidemiology and Etiology

Ureteropelvic junction (UPJ) obstruction occurs when the flow of urine from the renal pelvis to the ureter is restricted. If left uncorrected it will lead to progressive renal deterioration. UPJ obstruction may occur in all age groups; however, a biphasic distribution is found in the neonatal period because of the detection of antenatal hydronephrosis and later in life due to clinical manifestation. UPJ obstruction is more common in boys than in girls and left-sided lesions predominate; however, bilateral UPJ obstruction is present in 10–40%. Underlying causes are classified as primary and secondary UPJ obstruction. The exact pathogenesis of primary congenital UPJ obstruction is unknown. Primary intrinsic UPJ obstruction demonstrates a narrowed UPJ, which may be the result of a disrupted development of the circular musculature and extracellular matrix. Other intrinsic causes are valvular mucosal folds, persistent fetal convolutions, and upper ureteral polyps. The most common cause of extrinsic obstruction is an accessory lower pole vessel, which passes anteriorly to the UPJ and causes mechanical obstruction; it is a major cause of UPJ obstruction in adults. Secondary UPJ obstruction is associated with high-grade VUR in 10%, due to ureteral dilation and kinking. The treatment algorithm for secondary UPJ obstruction and VUR stipulates to relieve the obstruction first; endoscopic treatment of obstruction and VUR in the same setting may be considered. UPJ obstruction is frequently associated with other urinary tract anomalies. Contralateral UPJ obstruction is found in 10–40% of cases and renal dysplasia and multicystic dysplastic kidney are the next most common anomalies. UPJ obstruction can occur in a duplicated system, horseshoe kidney, or ectopic kidney. UPJ obstruction occurs in 9% of children with VATER association and is found with renal agenesis in 5%. VUR occurs in 40% of children, often low-grade with high likelihood of spontaneous resolution. UPJ obstruction is the most common cause of prenatal hydronephrosis (48%) followed by multicystic dysplastic kidney.

Presentation and Diagnosis

Most infants were diagnosed by prenatal sonography and are asymptomatic. Urinary tract infection is the leading symptom in children beyond the neonatal period (30%). UPJ obstruction is less frequently seen during childhood and adolescence and is most often caused by aberrant lower pole parenchymal vessels that cross over the UPJ. In older children, intermittent flank pain (Dietl's crisis) with or without nausea and vomiting is the prominent symptom. Hematuria may occur after mild abdominal trauma in 25% of children. In the young adult, intermittent flank pain associated with increased diuresis is most common. Rarely, hypertension is the presenting symptom. The underlying principle for the determination of obstruction by imaging studies is delayed excretion of contrast agents/tracers in a dilated urinary system. Based on abnormal prenatal US findings, a postnatal US is obtained between 2 and 4 weeks of life to allow improvement of the newborn's physiologic dehydration. Further evaluation includes a voiding cystourethrogram (VCUG) to rule out concurrent VUR. US cannot diagnose obstruction but high-grade or worsening hydronephrosis suggests obstruction. Refined ultrasonic methods may further improve the accuracy of diagnosis but are infrequently utilized (renal parenchyma to pelvocaliceal area index of less than 1.6; resistive index of $\geq$0.75) (*2*, *3*). Radionuclide renography is the most commonly obtained study to assess renal function and the degree of renal obstruction. The method of choice is a well-tempered renogram, which requires sufficient hydration and catheter placement (*4*). No consensus exists whether to administer the diuretic prior, at, or after injection of tracer material. ^{99m}Tc-MAG-3 is the preferred radiotracer because it provides higher image quality and more accurate values than ^{99m}Tc-DTPA because it remains essentially within the intravascular

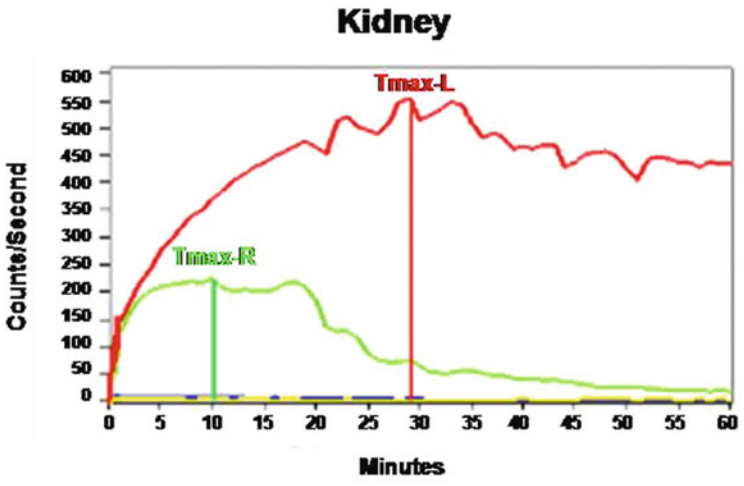

Fig. 15.1. MAG-3 renogram of a 17-month-old girl with L grade 3 hydronephrosis. L DRF 47%, R DRF 53%, R T1/2 14 min, L T1/2 >30 min.

space (Fig. 15.1). A half-time clearance of radioisotope of longer than 20 min denotes obstruction, whereas a half-time clearance of less than 10 min is consistent with a non-obstructed system. Indeterminate results range from 10 to 20 min and the renal scan may be repeated after several months; a further decline in differential renal function would be consistent with obstruction. Magnetic resonance urography (MRU) allows evaluation of morphology, vascular anatomy, renal function, and drainage in a single study. Gadolinium-DTPA serves as tracer molecule and can be observed as it transits through the renal parenchyma on serial image acquisitions. The renal transit time (RTT) is the time from first tracer appearance in the renal cortex to its appearance just distal to the UPJ. A RTT of less than 4 min is consistent with normal drainage. A RTT between 4 and 8 min denotes equivocal findings and a RTT of longer than 8 min obstruction. MRU does not employ ionizing radiation so that multiple studies may be obtained to follow hydronephrosis (*5*). Whitaker studies are in general not performed but may be useful in cases of equivocal findings or recurrent UPJ obstruction. After placement of a percutaneous renal catheter and bladder catheter, the renal pelvis is perfused with dilute contrast at a rate of 10 ml/s. Differential pressure of renal pelvis and bladder is determined. Pressure differences less than 15 cm H_2O are found in non-obstructed systems, 15–20 cm H_2O are equivocal, and more than 20 cm H_2O indicates obstruction.

Management and Complications

Management of UPJ obstruction comprises observation and surgery. Given the wide clinical spectrum of UPJ obstruction, it is very difficult to determine which patient will benefit from intervention and in whom it is not needed. Indications for surgical treatment are obstruction defined by excretory studies, diminished or worsening differential renal function on sequential studies (<40%), and clinical symptoms (e.g., febrile UTI, hematuria). The surgical technique most commonly applied today is the Anderson-Hynes dismembered pyeloplasty due to its broad applicability, which includes preservation of accessory vessels, excision of the UPJ, and reduction pyeloplasty. Since diuretic renograms do not demonstrate the UPJ and ureter, a retrograde pyelogram (RPG) is performed at the time of the pyeloplasty. The RPG may be omitted if the anatomy is well visualized preoperatively on MRU or IVP. Open surgical approaches include subcostal, flank, and dorsal lumbotomy. The dorsal lumbotomy approach is appropriate in children less than 2 years but not in the muscular adolescent. The open dismembered pyeloplasty is well tolerated by young children and the benefits of laparoscopy not readily apparent. Principles of dismembered pyeloplasty include excision of the narrowed UPJ, spatulation of the ureter, optional placement of ureteral stent and Penrose drain, Foley catheter for 1–2 days, and anastomosis with absorbable suture. Lower pole UPJ obstruction can occur in incomplete renal duplications and is treated depending on the length

of ureter distal to the UPJ with either a dismembered pyeloplasty (long ureter) or a pyeloureterostomy. Minimally invasive techniques include endoscopic approaches and laparoscopic pyeloplasty. Endoscopic treatment of UPJ obstruction can be performed in the adolescent and preadolescent child in an antegrade and retrograde fashion. The retrograde method of choice utilizes the Acucise device (ureteral cutting balloon catheter) for endopyelotomy. Antegrade endopyelotomy can be achieved under direct vision with a cold knife, electrocautery, or laser. A ureteral stent is left for 6 weeks. An ideal situation for endopyelotomy is the failed pyeloplasty because the UPJ is in dependent position and narrowed by a stricture, and a nephrostomy tube is already in place (*6*). Laparoscopic pyeloplasty can be performed via transperitoneal and retroperitoneal approaches. Robotically assisted pyeloplasty overcomes the difficult laparoscopic suturing and therefore makes pyeloplasty available to surgeons without advanced laparoscopic experience (*7*). Early complications include prolonged urinary drainage from the Penrose drain, which in general improves with observation. If it persists beyond 14 days, a ureteral stent may help. If a patient presents postoperatively with fever, pain, and significant hydronephrosis, a nephrostomy tube is necessary. Lack of drainage for a prolonged time necessitates further intervention (endopyelotomy, redo pyeloplasty, ureterocalicostomy).

PREURETERAL VENA CAVA

This anomaly is also known as circumcaval or retrocaval ureter and involves the right ureter, which courses posteriorly to the inferior vena cava (IVC) and crosses from a medial to lateral direction anteriorly. The anomaly is caused by persistence of the subcardinal vein in the lumbar portion trapping the ureter dorsally. The incidence is 1:1500, 3–4 times more common in males than in females. The more common type I produces hydronephrosis secondary to obstruction with a fishhook-shaped deformity of the ureter. The type II ureter passes behind the IVC at a higher level and causes less obstruction and hydronephrosis. Although a congenital lesion, patients do in general not present until the third or fourth decade of life with symptoms of flank pain and UTI. Diagnosis is made with US, CT scan, or MRI, which can define the vascular anatomy. Treatment of choice is the Anderson-Hynes dismembered pyeloplasty, originally described in a case of preureteral vena cava. The retrocaval segment may be aperistaltic and needs to be excised.

VASCULAR OBSTRUCTION OF THE DISTAL URETER

A retroiliac ureter (preureteral iliac artery) passes posteriorly to the common iliac artery, is rare, and obstruction unusual. The condition is found with equal frequency on both sides and can occur bilaterally. Associated

genitourinary anomalies are frequently encountered such as ureteral ectopia or ectopia of the vas deferens. Obstruction of the distal ureter by uterine, umbilical, obturator, and internal iliac vessels has been described.

URETERAL STENOSIS AND STRICTURE

A ureteral stenosis is defined as congenital narrowing of the ureteral lumen whereas a ureteral stricture implies a secondary etiology. The pathogenesis of a ureteral stenosis is unknown but is most likely caused by a disrupted mesenchymal development of ureteral musculature. The area with the highest incidence of ureteral stenosis is the UPJ followed by the distal ureter just above the ureterovesical junction (UVJ), and rarely the mid-ureter at the pelvic brim; multiple areas may be affected. The clinical manifestations, diagnosis, and treatment options depend on the level of stenosis.

URETERAL VALVES

Ureteral valves are transverse folds of redundant mucosa, which contain smooth muscle and are an uncommon cause of obstruction. Ureteral valves are diaphragmatic or annular lesions with a pinpoint opening. The ureter is dilated above and normal below it. The valves are distributed throughout the length of the ureter, least common in the midureter or at the UPJ. Symptoms include flank pain, UTI, incontinence, and hematuria. Ureteral valves are distinct from mucosal folds and may be formed secondary to an underlying obstruction by elongation, dilation, and kinking of the ureter. Treatment options of ureteral valves comprise resection, primary anastomosis, and, if renal function is significantly impaired, nephrectomy.

PERSISTENT FETAL FOLDS

Persistent fetal folds (Oestling's folds) are a common finding in the third trimester and may persist until the newborn period in 5% of ureters and gradually disappear with growth. Such folds are mucosal in-folds which do not flatten when the ureter is stretched. Fetal folds are caused by differential ureteral and body growth, represent a length reserve, and are in general not obstructive. Persistent fetal folds, which contain muscle and act as a valvular leaflet at the UPJ may become obstructive. Ureteral obstruction may be relieved by dissection of the affected ureteral segment and elimination of kinking, however, more commonly requires excision.

ECTOPIC URETER

Epidemiology and Etiology

An ectopic ureter inserts into the bladder neck or more distally into mesonephric or paramesonephric duct derivatives with variable frequency

Table 15.3
Ectopic ureteral insertion sites in boys and girls

Males	
Posterior urethra	47%
Seminal vesicle	33%
Prostatic utricle	10%
Ejaculatory duct	5%
Vas deferens	5%
Females	
Urethra	35%
Vestibule	34%
Vagina	25%
Cervix or uterus	5%

(Table 15.3). As a general rule, the more remote ureteral insertion is associated with a higher degree of renal hypoplasia and dysplasia. An ectopic ureter may be severely obstructed causing massive hydroureteronephrosis. In girls the majority of ectopic ureters (80%) are associated with a duplicated system; in boys most ectopic ureters drain a single system. Ectopic ureters are found bilaterally in 5-15% and with a unilateral ectopic ureter a contralateral duplicated system is not uncommon. Ectopic ureters may occur with anomalies of the internal genitalia such as duplicated vaginas, hemivaginas, and bicornuate uteruses.

Presentation and Diagnosis

Continuous incontinence or persistent vaginal discharge in a girl without voiding dysfunction after toilet training is the classic symptom of an ectopic ureter because the ureter inserts distal to the urinary sphincter. Patients with ectopic ureters into the proximal urethra often experience VUR and urge incontinence. In boys all extravesical insertions are proximal to the external sphincter and do therefore not produce urinary incontinence, however, they often present with UTI or epididymitis. Ectopic ureters are readily seen on prenatal US and identified by hydroureteronephrosis secondary to obstruction. Postnatal evaluation confirms the diagnosis. Physical exam in girls may demonstrate continuous dribbling and sometimes an orifice is identified at the urethrovaginal septum. US shows hydronephrosis of a single or duplicated system with a hydroureter posterior to a normal bladder. While MAG-3 renography provides renal function and drainage data, MRU acquires both functional/drainage and anatomical information (Fig. 15.2). In 50% of cases, VUR into the lower pole is seen and sometimes into the ectopic ureter. VUR during storage implies an orifice proximal to the bladder neck and VUR

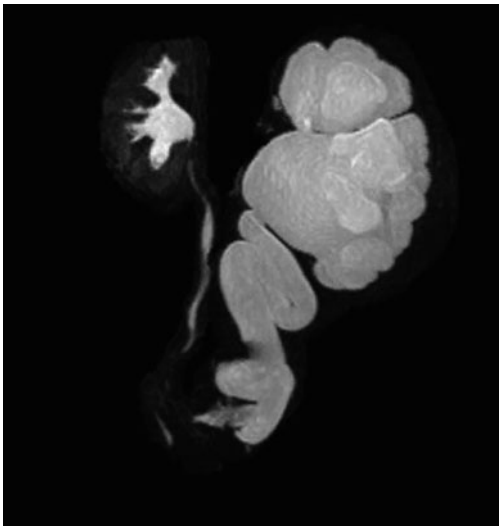

Fig. 15.2. MRU (T2-weighted image) of L ectopic ureter with hydroureteronephrosis in a 4-month-old boy. R DRF 82%, L DRF 18%, R RTT 6 min, L RTT >25 min.

with voiding a distal orifice. Ectopic ureteral orifices may be identified by cystoscopy and vaginoscopy and a ureteral catheter can be placed in order to obtain an RPG.

Management

The majority of ectopic ureters drain minimally functioning renal moieties and upper pole heminephrectomy is indicated. In some cases renal function is worth salvaging with either ureteropyelostomy or common/single sheath ureteral reimplantation. Postoperatively, anatomy and function of the lower pole are evaluated with a nuclear renogram or MRU. Surgical alternatives are laparoscopic nephrectomy or heminephrectomy through a transabdominal or retroperitoneal approach, or robotically assisted laparoscopy. If the ureteral orifice inserts proximal to the sphincter, endoscopic dilation of the orifice may relieve the obstruction (*8*).

URETERAL FILLING DEFECTS

Renal papillary necrosis is uncommon in the pediatric population except in patients with sickle cell disease, and may occur secondary to hypoxia, dehydration, and sepsis. When necrotic renal papillae slough, unilateral or bilateral ureteral obstruction can develop, and ureteral stent or percutaneous nephrostomy placement becomes necessary.

In children with disseminated candidiasis the kidney is the most commonly affected organ. Predisposing factors for fungemia include antibiotic

treatment, prematurity, vascular catheters, parenteral nutrition, and immunocompromised status. Fungal bezoars may form in the renal pelvis causing obstruction or anuria in cases of bilateral involvement. Although urinary alkalinization and IV antifungals can dissolve fungal balls, some patients may require percutaneous access for local irrigation or removal.

Blood clots most commonly seen after percutaneous renal biopsy may cause ureteral obstruction in children. Ureteral catheter placement is the treatment of choice; however, clot resolution by infusion of streptokinase via ureteral catheter has been described (*9*).

Most filling defects of the upper collecting system represent benign conditions. The most common lesion is a fibroepithelial polyp. Patients present with symptoms of obstruction (flank pain, hematuria) and management consists of segmental resection and ureteral reconstruction. Recently, percutaneous resection was shown to be an effective treatment option.

URETEROCELE

Epidemiology and Etiology

A ureterocele is defined as a cystic dilatation of the terminal ureter. The location of an intravesical ureterocele is entirely within the bladder, whereas an ectopic ureterocele extends to the bladder neck or further distally. Ureteroceles are more frequently found in girls (4:1) and almost exclusively in Caucasians. Eighty percent are associated with the upper poles of duplicated systems, 10% are bilateral, whereas single system ureteroceles are usually found in adults.

Presentation and Diagnosis

Children with ureteroceles most commonly present with UTI or urosepsis and should consequently receive antibiotic prophylaxis. Physical exam may reveal significant hydronephrosis and sometimes demonstrate a prolapsed ectopic ureterocele. If the ureterocele is large enough it can obstruct the bladder neck or the contralateral ureteral orifice and result in bilateral hydroureteronephrosis. Ectopic ureteroceles can cause incontinence by inhibiting normal sphincteric function. Ureteroceles are often diagnosed by prenatal US. Postnatal US demonstrates most commonly a duplicated kidney with upper pole hydroureteronephrosis, and a ureterocele within the bladder. The ureterocele may be missed if the bladder is overdistended and the ureterocele effaces, or if the bladder is empty and the ureterocele is interpreted as partially filled bladder. A minute upper pole moiety can go unnoticed with a large ureterocele (ureterocele disproportion). A large hydroureter posterior to the bladder may be mistaken for a ureterocele (pseudoureterocele). Signs of a duplicated system on IVP are a poorly functioning upper pole, lateral deviation, drooping-lily sign, and reduced number of calyces. VCUG demonstrates the ureterocele and presence of VUR in general in the

ipsilateral lower pole unit. Up to 30% of patients have contralateral VUR due to distortion of the bladder trigone. VUR into the ureterocele is uncommon and happens more commonly when an ectopic ureterocele opens into the urethra. VCUG images should be obtained at early filling stages because ureteroceles efface and may evert at later filling stages and appear as bladder diverticula. If the side of a ureterocele is indeterminate, contrast can be injected during cystoscopy. Radionuclide radiographies are used to evaluate renal function and the degree of obstruction.

Management

The goals of treatment are manifold and include preservation of renal function, elimination of infection, obstruction, and reflux, maintenance of urinary continence, and minimizing surgical morbidity. Early institution of antibiotic prophylaxis is paramount. The upper tract approach (upper pole nephrectomy and partial ureterectomy, ureteropyelostomy) aims at decompressing the ureterocele and spontaneous resolution of the ipsilateral VUR. In cases of high-grade VUR, everting ureterocele, or ectopic ureterocele, a combined upper tract and lower tract approach is necessary because VUR is less likely to resolve. For patients likely requiring a secondary procedure (high-grade VUR, prolapsed ureterocele), septic patients not responding to antibiotics, and ureteroceles causing bladder outlet obstruction, a ureterocele puncture is recommended. Ureterocele puncture is performed with a 3-French Bugbee electrode near the base of the ureterocele and proximal to the bladder neck. The goal is to relieve the obstruction and to allow the collapsed ureterocele to act as a flap valve in order to prevent VUR. Endoscopic punctures of ectopic ureteroceles are less successful than of intravesical ureteroceles. The lower tract approach consists of ureterocele excision and common sheath ureteral reimplantation. An alternative treatment option is to relieve obstruction in a functioning upper pole by ureteroureterostomy or pyeloureterostomy.

Single System Ureteroceles

Single system ureteroceles are usually found in adults and rarely seen in children. They are almost always found in orthotopic position and obstruction tends to be less severe than in ureteroceles associated with a duplicated system. Urinary stasis and UTI predispose patients to stone formation within the ureterocele and upper urinary tract. The cobra-head deformity is the classic sign of a single system ureterocele on IVP. Upper urinary tract changes are usually mild. Single system ureteroceles are amenable to endoscopic puncture with a lower incidence of postoperative VUR. Alternatively, transvesical ureterocelectomy with ureteral reimplantation may be performed.

Prolapsing Ureteroceles

Ureteroceles can prolapse through the bladder neck and urethra and present as vaginal masses. Prolapsing ureteroceles can be distinguished from other interlabial masses (rhabdomyosarcoma, urethral prolapse, hydrometrocolpos, periurethral cyst) on physical exam. A prolapsed ureterocele appears spherical; the surface is smooth and usually pink. Prolapsing ureteroceles may cause bladder outlet obstruction and the first line treatment is manual reduction; however, recurrence is likely. A urethral catheter can be placed anteriorly to the ureterocele. In an acutely obstructed child a ureterocele incision or transurethral incision should be attempted; if still obstructed open unroofing or ureterocelectomy will be successful with elective ureteral reimplantation.

URETEROVESICAL JUNCTION OBSTRUCTION

Epidemiology and Etiology

Ureterovesical junction (UVJ) obstruction produces dilation of the renal pelvis and ureter (hydroureteronephrosis). A hydroureter is defined as a ureteral diameter greater than 5 mm whereas ureters wider than 7–8 mm are considered megaureters irrespective of their underlying etiology (i.e., VUR and/or obstruction). UVJ obstruction accounts for 25% of prenatally detected cases of urinary tract dilatation. Causes of UVJ obstruction can be classified as primary and secondary. The most common finding of a primary obstructed megaureter is an aperistaltic juxtavesical (adynamic) ureteral segment that prevents normal urine flow. Abnormal development and alignment of ureteral smooth muscle cells with increased deposition of collagen at the UVJ manifest in irregular and insufficient peristalsis (ureteroarrythmias). Secondary causes of UVJ obstruction produce a relative narrowing at the UVJ, such as bladder outlet obstruction with detrusor hypertrophy (e.g., posterior urethral valves, neurogenic bladder), periureteral post-reimplantation fibrosis, chronic urinary tract infections with transmural scarring, or external compression by retroperitoneal masses. Iatrogenic UVJ obstruction may occur after anti-reflux procedures. Bilateral ureteral obstruction after endoscopic treatment is rare (0.6%). Factors that may increase the risk of obstruction after injection treatment are voiding dysfunction and abnormally dilated ureters. A small group of patients with UVJ obstruction exhibits also an element of reflux. In such ureters a dysplastic distal segment not only fails to coapt the intramural tunnel but also lacks effective peristalsis.

Diagnosis and Management

The incidence of refluxing and obstructed ureters is approximately 2% of patients with VUR. Prenatal US readily demonstrates hydroureteronephrosis

and a VCUG and renal drainage study will establish the diagnosis. Secondary UVJ obstructions are treated according to their etiologies and are initially managed with ureteral stent or nephrostomy tube placement.

POSTERIOR URETHRAL VALVES

Epidemiology and Etiology

The incidence of posterior urethral valves (PUV) is 1 in 5,000–8,000 live births, which accounts for approximately 10% of all prenatally detected cases of urinary tract obstruction. PUV are classified as type I and type III valves (Young classification); however, presentation, diagnosis, treatment, and prognosis are similar. Type I valves comprise 95% of all PUVs and are leaflets, which extend from the verumontanum distally across the entire anterior circumference of the urethra leaving only a small channel along the posterior wall. Type II valves are no longer regarded as valves. Type III valves are diaphragmatic membranes distal to the verumontanum with a small central opening. The sequelae of congenital PUV are seen at all levels proximal to the obstruction secondary to high voiding pressure. The prostatic urethra is dilated and the bladder neck is hypertrophied and rigid. Detrusor muscle hypertrophy leads to bladder wall thickening and deterioration of bladder compliance. All PUV patients demonstrate hydroureteronephrosis and 50% have VUR. Various degrees of renal dysplasia (irreversible) and uropathy (reversible) are found. Prognostic indicators for long-term renal function are listed in Table 15.4 (*10*).

Table 15.4
Prognostic indicators for poor renal function

Renal ultrasound	Hyperechogenicity Loss of corticomedullary differentiation
Age at diagnosis	Presentation <1 year of age
Vesicoureteral reflux	Bilateral
Serum creatinine	Nadir creatinine >0.8 mg/dl

Presentation and Diagnosis

Sixty percent of patients present with tubular damage, which manifests as failure to concentrate and to eliminate urinary acids. Tubular damage worsens with age and high urine volumes contribute to the deterioration of renal and bladder function. Elevated voiding pressures cause pop-off mechanisms such as VUR, bladder diverticula, urinary ascites, and a patent urachus. Unilateral VUR that is associated with renal dysplasia is termed VURD syndrome (Valve Unilateral Reflux Dysplasia); its protective effect on renal function is controversial. Clinical manifestations of PUVs depend on the

age of presentation. The most significant clinical problem of the neonate is pulmonary hypoplasia secondary to oligohydramnios accounting for most of the neonatal mortality. Urinary sepsis, renal insufficiency, and ascites are other common symptoms in the newborn period. The majority of older boys present with UTIs and/or voiding dysfunction. Most of PUVs are diagnosed with prenatal US. Classic US findings include bilateral hydroureteronephrosis, distended bladder and dilated posterior urethra ("keyhole sign"), as well as a thickened bladder wall. VCUG confirms the diagnosis by demonstrating a trabeculated bladder, elevated bladder neck, and dilated posterior urethra. Radionuclide renal scans can provide valuable information regarding differential renal function and renal drainage.

Management

PUV management begins with immediate bladder drainage. Five French feeding tubes are preferred to Foley catheters because the latter can induce significant bladder spasms with consecutive functional UVJ obstruction. Once the patient is stabilized, endoscopic valve incision is performed with a Bugbee electrode, resectoscope, Laser, or cold knife at the 4 o'clock, 8 o'clock, and sometimes 12 o'clock position (Fig. 15.3). Continued catheter drainage for 24 h reduces the risk for hematuria but is not imperative. If valve ablation cannot be performed (e.g., neonate too small for instrumentation), a vesicostomy is indicated. Upper urinary tract diversion (ureterostomy, pyelostomy) is reserved for patients who fail to respond to bladder drainage and continue to experience urinary tract infections, elevated creatinine (>2 mg/dl after 10 days of bladder drainage), and worsening hydroureteronephrosis. Up to 30% of VUR will resolve spontaneously once the obstruction is relieved and antibiotic prophylaxis is indicated for all cases of reflux. Persistent VUR is in general propagated by high voiding pressure and requires bladder evaluation by a videourodynamic study. If urodynamic parameters are appropriate, an anti-reflux procedure is indicated. A "valve bladder" describes a chronic condition in patients after adequate valve ablation that will lead to deterioration of the upper urinary tracts and to urinary incontinence. Patients with PUV commonly present with prolonged daytime and nighttime incontinence up to 20 years of age.

ANTERIOR URETHRAL VALVES

Obstruction secondary to anterior urethral valves (AUV) is rare compared to PUV. Although called AUV, the underlying pathology of AUV is a urethral diverticulum with its distal wall acting as a flap that may obstruct the flow of urine. AUV develop secondary to defects of the corpus spongiosum with consecutive diverticulum formation. Patients usually present later in life with UTI, incontinence, or straining. The clinical manifestation of AUV may be as severe as with PUV. AUV are diagnosed by VCUG or cystoscopy

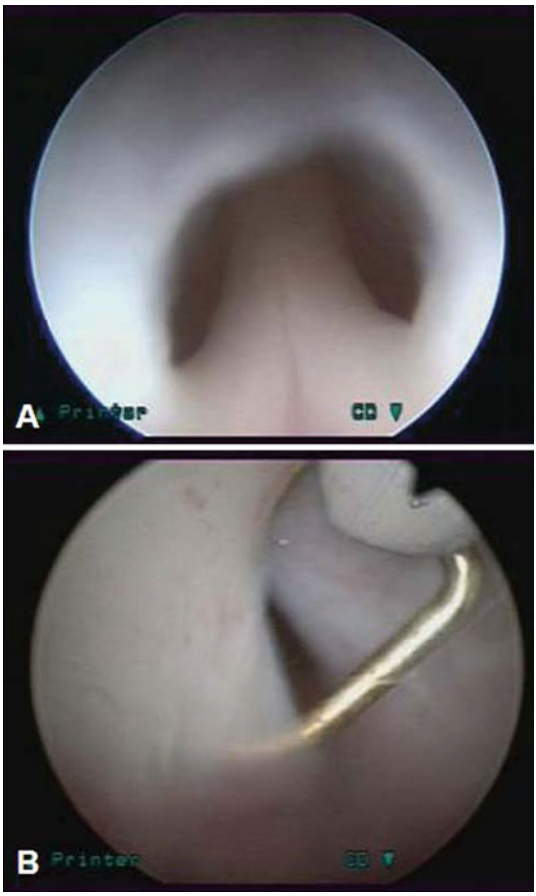

Fig. 15.3. (**a**) Cystoscopic view of PUVs. (**b**) Endoscopic incision.

and treated with endoscopic resection or urethral reconstruction depending on the size of the diverticulum. The long-term prognosis, however, seems to be more favorable for anterior than posterior urethral valves with ESRD occurring in 5 and 30%, respectively.

CONGENITAL URETHRAL STRICTURE

Congenital urethral strictures are rare causes of obstruction within the posterior urethra. Prenatal findings and postnatal symptoms are identical with PUV. Primary treatment is vesicostomy because congenital urethral strictures are generally long and not amenable to endoscopic incision. Progressive urethral dilation with catheters has shown promising results (*11*).

URETHRAL ATRESIA

Urethral atresia is defined as a complete luminal obliteration of the posterior urethra and is often associated with hypoplasia of the distal urethral segment. Urethral atresia is rare and occurs most commonly in patients with prune-belly syndrome. It is incompatible with life unless alternative communications exist such as a patent urachus or a rectourethral fistula. Vesicostomy is the primary treatment of choice because outcome with urethral dilation has been poor. Most patients will need a continent catheterizable stoma and eventually require kidney transplantation (*12*).

REFERENCES

1. Seikaly, M.G., Ho, P.L., Emmett, L., Fine, R.N., and Tejani, A. (2003) Chronic renal insufficiency in children: the 2001 Annual Report of the NAPRTCS. *Pediatr Nephrol* 18, 796–804.
2. Gilbert, R., Garra, B., and Gibbons, M.D. (1993) Renal duplex Doppler ultrasound: an adjunct in the evaluation of hydronephrosis in the child. *J Urol* 150, 1192–4.
3. Cost, G.A., Merguerian, P.A., Cheerasarn, S.P., and Shortliffe, L.M. (1996) Sonographic renal parenchymal and pelvicaliceal areas: new quantitative parameters for renal sonographic followup. *J Urol* 156, 725–9.
4. Conway, J.J. and Maizels, M. (1992) The "well tempered" diuretic renogram: a standard method to examine the asymptomatic neonate with hydronephrosis or hydroureteronephrosis. A report from combined meetings of The Society for Fetal Urology and members of The Pediatric Nuclear Medicine Council – The Society of Nuclear Medicine. *J Nucl Med* 33, 2047–51.
5. Kirsch, A.J., McMann, L.P., Jones, R.A., Smith, E.A., Scherz, H.C., and Grattan-Smith, J.D. (2006) Magnetic resonance urography for evaluating outcomes after pediatric pyeloplasty. *J Urol* 176, 1755–61.
6. Tallai, B., Salah, M.A., Flasko, T., Toth, C., and Varga, A. (2004) Endopyelotomy in childhood: our experience with 37 patients. *J Endourol* 18, 952–8.
7. Lee, R.S., Retik, A.B., Borer, J.G., and Peters, C.A. (2006) Pediatric robot assisted laparoscopic dismembered pyeloplasty: comparison with a cohort of open surgery. *J Urol* 175, 683–7.
8. Akbal, C., Lee, S.D., and Kaefer, M. (2004) Minimally invasive retrograde endourological technique for obstructed ectopic ureter. *J Urol* 172, 1445.
9. Stegmayr, B. and Orsten, P.A. (1984) Lysis of obstructive renal pelvic clots with retrograde instillation of streptokinase. A case report. *Scand J Urol Nephrol* 18, 347–50.
10. Warshaw, B.L., Hymes, L.C., Trulock, T.S., and Woodard, J.R. (1985) Prognostic features in infants with obstructive uropathy due to posterior urethral valves. *J Urol* 133, 240–3.
11. Passerini-Glazel, G., Araguna, F., Chiozza, L., Artibani, W., Rabinowitz, R., and Firlit, C.F. (1988) The P.A.D.U.A. (progressive augmentation by dilating the urethra anterior) procedure for the treatment of severe urethral hypoplasia. *J Urol* 140, 1247–9.
12. Gonzalez, R., De Filippo, R., Jednak, R., and Barthold, J.S. (2001) Urethral atresia: long-term outcome in 6 children who survived the neonatal period. *J Urol* 165, 2241–4.

16 Tissue Engineering and Regenerative Medicine – Current Concepts

Anthony Atala

Abstract Many common congenital abnormalities, such as hypospadias, epispadias, and bladder exstrophy, involve the genitourinary system. Children with these conditions often require immediate and/or multiple reconstructive surgeries. Currently, urologic and genital reconstruction may be performed with autologous non-urologic tissues (skin, gastrointestinal segments, or mucosa), homologous tissues from a donor (cadaver or living donor kidney), heterologous tissues or substances (bovine collagen), or artificial materials (silicone, polyurethane, or Teflon). However, these materials often lead to complications after reconstruction, either because the implanted material is rejected or because inherently different functional parameters cause a mismatch in the system. For example, replacement of bladder tissue with gastrointestinal segments can be problematic due to the opposite ways in which these two tissues handle solutes – urologic tissue normally excretes material, and gastrointestinal tissue generally absorbs the same materials. This mismatched state can lead to metabolic complications as well as infection and other serious issues. The replacement of lost or deficient urologic tissues with functionally equivalent ones would significantly improve the outcome of reconstructive surgery in the genitourinary system. This may soon be possible using novel techniques developed with tissue engineering and regenerative medicine strategies.

Keywords Genitourinary reconstruction · Tissue engineering · Biomaterials · cell therapy · Regenerative medicine · Transplantation · Organ substitutes · Stem cells

AN INTRODUCTION TO REGENERATIVE MEDICINE AND TISSUE ENGINEERING STRATEGIES

Regenerative medicine is a discipline that combines techniques such as cell transplantation, material science, and bioengineering to construct

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biological substitutes for organs and tissues. The goal is to prolong life by reducing mortality from organ failure as well as to increase the quality of life for those who require organ transplantation and reconstructive surgeries. It involves the development of methods to activate the body's latent ability to regenerate tissues and organs, as well as the development of laboratory-grown organ substitutes which could restore and maintain normal cell, tissue, and organ function. These techniques involve the use of specialized biomaterials, specific cells, or both.

BIOMATERIALS

Currently, most strategies for tissue construction include the use of novel biomaterials. Biomaterials are a class of biocompatible materials that can be fabricated from synthetic materials, naturally derived substances, or both combined, and they can be configured into liquid, gel, or solid forms depending on specific needs. These may be used alone as scaffolds that the body can use as a blueprint for regeneration of functional tissue. Alternatively, biomaterials can be used as support matrices for cells. This type of matrix is seeded with cells ex vivo. Then, the cell-containing matrix is implanted into a patient and allowed to form a functional tissue or organ. Still other types of biomaterials may serve as cell carriers (e.g., the use of hydrogels to deliver cells to a target location in the body) or delivery vehicles for macromolecules such as growth factors and cytokines.

These materials are designed to replicate the biologic and mechanical functions of the native extracellular matrix (ECM) found in tissues in the body. They provide a three-dimensional structure to which cells can attach and form new tissues with appropriate shape and function. As the majority of mammalian cell types are anchorage-dependent, the cell-adhesion properties of these biomaterials are essential to the success of these implants. In addition to that very important role, biomaterials allow the delivery of cells to specific sites in the body with adequate loading efficiency and provide structural support against in vivo forces so that the predefined three-dimensional structure of the scaffold (what will eventually become the tissue or organ's "shape") is maintained during tissue development. Furthermore, bioactive signals, such as cell-adhesion peptides and growth factors, can be incorporated into the biomaterial scaffold to help regulate cellular function during development (*1*, *2*). Some novel materials are designed to carry these factors into the body and release them at a specified rate to assist the cells in the organizational phase of development.

With these functions in mind, it is clear that the ideal biomaterial should be biodegradable and bioresorbable, so that the material can support the replacement of normal tissue only as long as necessary. In addition, biomaterials must be non-immunogenic to avoid inflammatory responses and rejection. A number of materials have been developed that fit these criteria. The most commonly used biomaterials in regenerative medicine include (*1*)

naturally derived materials (e.g., collagen and alginate), (*2*) acellular tissue matrices (e.g., bladder submucosa and small intestinal submucosa), and (*3*) synthetic polymers of α-hydroxy acids (e.g., polyglycolic acid (PGA), polylactic acid (PLA), and poly lactic-co-glycolic acid (PLGA)). These classes of biomaterials have been tested with respect to their biocompatibility (*3*, *4*). Naturally derived materials and acellular tissue matrices have the potential advantage of biological recognition and thus, better biocompatibility. However, synthetic polymers can be prepared reproducibly on a large scale, and properties such as strength, degradation rate, and microstructure can be controlled during the manufacturing process.

CELLS

Many tissue engineering techniques also involve cell transplantation. The cells used for this purpose can be derived from autologous, allogeneic, or xenogeneic sources, and cells at various developmental stages, from embryonic stem cells to fully differentiated somatic cells, are currently being studied. The most common source of cells for tissue engineering applications is a small piece of autologous tissue, such as a biopsy. This piece of tissue is dissociated into individual cells in the laboratory. At this point, the cells can be implanted directly into the host, or they can be expanded in culture and attached to a support matrix made from a biomaterial. Then, the cell/matrix combination is reimplanted into the host. The use of autologous cells in this procedure promotes structural and functional tissue replacement with minimal complications (*5*–*10*). While a self-limiting inflammatory response may occur, the use of autologous cells circumvents rejection and would obviate the need for immunosuppressant medications after transplantation of the engineered organ.

However, in the past, it was not known if a sufficient number of cells could be generated to create an organ in certain cases. For example, it was thought that diseased organs may not contain enough normal cells to begin the process of cell culture. However, recent research suggests that this may not be the case. For example, one study has shown that cultured neuropathic bladder smooth muscle cells possess and maintain different characteristics than normal smooth muscle cells in vitro, as demonstrated by growth assays, contractility, and adherence tests (*11*). However, despite these differences, when neuropathic smooth muscle cells were cultured in vitro and then seeded onto matrices and implanted in vivo, the tissue engineered constructs that developed showed the same properties as constructs engineered with normal cells (*12*). It is now known that genetically normal progenitor cells, which are the reservoirs for new cell formation, are present even in diseased tissue. These normal progenitors are programmed to give rise to normal tissue, regardless of whether they reside in a normal or diseased environment. Therefore, the progenitor cell niche and its role in normal tissue regeneration remains a fertile area of ongoing investigation.

In addition, for many years, the difficulty of growing specific cell types in large quantities limited their use in tissue engineering applications. Even when certain organs, such as the liver, have a high regenerative capacity in vivo, in vitro expansion of cells derived from these organs has proven to be difficult. However, when privileged sites for committed precursor cells were discovered in these organs, the field was revolutionized. Intense study of the conditions that promote precursor cell maintenance and differentiation within these sites has produced important information about how these cells survive and grow. Many of these conditions have been replicated in the culture dish, allowing scientists to maintain populations of these cells in the laboratory. For example, scientists had made many attempts to grow urothelial cells from the bladder in culture in the past, but only with limited success. However, several novel culture protocols have been developed over the past two decades which allow urothelial precursor cells to be maintained in an undifferentiated state. Since the precursor cells can remain in the growth phase, the ability to expand urothelial cultures is vastly improved (*13*–*16*). These studies suggest that it may be possible to collect autologous urothelial cells from human bladders, expand them in culture, and return them to the patient in sufficient quantities for reconstructive purposes (*13*, *15*–*19*). In addition to urothelial cells, methods to induce the in vitro expansion of a variety of primary human cells have been developed, making the use of autologous cells for clinical applications a real possibility.

However, there are instances where autologous cells cannot be used for cell therapy because extensive organ damage or total loss of the tissue to be regenerated has occurred. In addition, cells from tissues containing malignancies cannot be used due to the threat of cancer recurrence in the regenerated tissue. In these cases, the use of other cell sources, such as allogeneic and xenogeneic cells, has been proposed, but these cells must be protected from host immune responses.

Stem cells are also an attractive cell source for these situations. They can be derived from different stages of development and, as they are able to self renew, they can result in large quantities of undifferentiated cells. Moreover, these undifferentiated cells have the ability to differentiate into many specialized cell types (*20*–*22*). For example, human embryonic stem cells (ES) can develop into cells comprising all three embryonic germ layers in vitro. Skin and neurons have been formed, indicating ectodermal differentiation (*23*–*25*). Blood, cardiac, cartilage, endothelial, and muscle cells have been produced, indicating mesodermal differentiation (*26*–*28*). Finally, pancreatic cells have been formed, indicating endodermal differentiation (*29*). Other stem cell sources that have been proposed and used for regenerative medicine therapies include fetal, amniotic fluid, and adult stem cells (*30*–*35*).

The process of nuclear transfer, or cloning, can serve as another source of pluripotent “stem” cells that could be used for regenerative medicine therapies. Two types of cloning procedures exist – reproductive cloning and

therapeutic cloning – and it is extremely important to differentiate between these two processes. Both involve the insertion of donor DNA, which usually comes from a somatic cell, into an enucleated oocyte. This generates an embryo that has identical genetic material to its DNA source. However, the similarities end there. In reproductive cloning, the embryo is then implanted into the uterus of a pseudopregnant female to produce an infant that is a clone of the donor. A world-famous example of this type of cloning resulted in the birth of a sheep named Dolly in 1997 (*36*). However, there are many ethical concerns surrounding such practices, and as a result, reproductive cloning has been banned in most countries.

While therapeutic cloning also produces an embryo that is genetically identical to the donor, this process is used to generate blastocysts that are explanted and grown in culture, rather than in utero. Embryonic stem cell lines can then be derived from these blastocysts, which are only allowed to grow up to a 100-cell stage. These stem cells are essentially autologous, and have the potential to become almost any type of cell in the adult body. Certainly, these cells would be useful in tissue and organ replacement applications (*37*). Therefore, therapeutic cloning, which has also been called somatic cell nuclear transfer (SNCT), may provide an alternative source of transplantable cells that are identical to the patient's own cells. This process is outlined in Fig. 16.1.

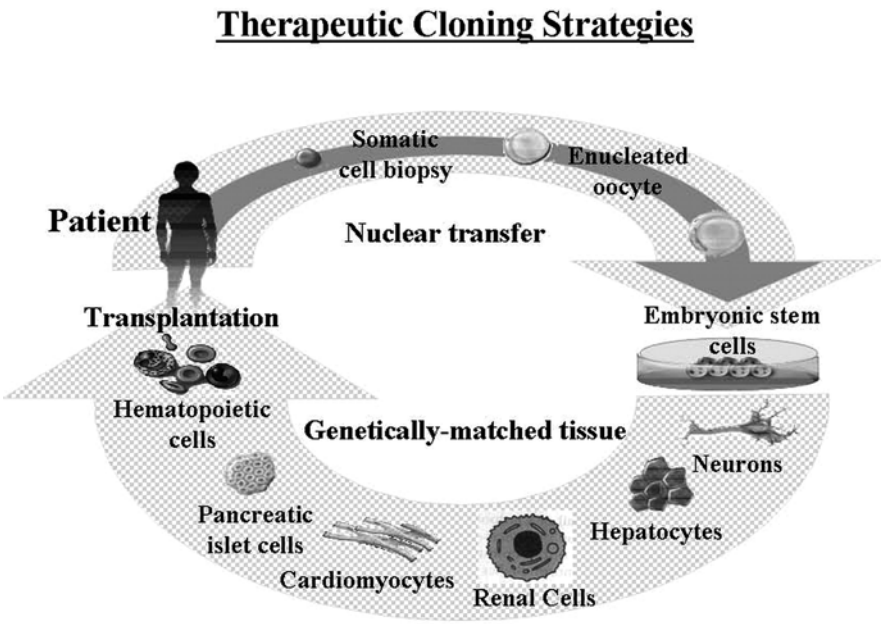

Fig. 16.1. Strategies for therapeutic cloning in regenerative medicine.

USING TISSUE ENGINEERING TECHNIQUES TO BUILD SPECIFIC UROLOGIC AND GENITAL STRUCTURES

Abnormalities of the genital and urinary tracts such as hypospadias, epispadias, and bladder exstrophy require multiple reconstructive surgeries. Currently, urologic and genital reconstruction may be performed with autologous non-urologic tissues, heterologous tissues or substances or artificial materials. However, reconstructive surgeries using these materials are often limited. In cases where autologous tissue is used, the amount of tissue available for use in reconstruction is usually limited, and donor site morbidity is a real concern. Further, use of foreign materials often leads to rejection or graft failure.

In recent years, the replacement of lost or deficient urologic tissues with functionally equivalent ones derived from tissue engineering protocols has been studied with great interest, as the development of biocompatible, functionally equivalent tissues would significantly improve the outcome of reconstructive surgery in the genitourinary system. Investigators around the world, including our laboratory, have been working toward the development of "laboratory grown" tissues and organs for clinical application. The following sections will describe this research in detail.

URETHRA

Various strategies have been proposed over the years for the regeneration of urethral tissue. Woven meshes of PGA (Dexon) have been used to reconstruct urethras in dogs (*38*). Also, PGA has been used as a cell transplantation vehicle to engineer tubular urothelium in vivo (*39*). Small-intestinal submucosa (SIS) without cells was used as an onlay patch graft for urethroplasty in rabbits (*40*). Finally, a homologous graft of acellular urethral matrix was also used in a rabbit model (*41*).

Bladder-derived acellular collagen matrix has proven to be quite suitable as a graft for repair of urethral defects in rabbits. In the rabbit model, neourethras created with these matrices demonstrated a normal urothelial luminal lining and organized muscle bundles shortly after repair (*40*, *41*). These results were confirmed clinically in a series of patients with a history of failed hypospadias reconstruction. In this study, the urethral defects were repaired with human bladder acellular collagen matrices (Fig. 16.2) (*42*, *43*). One the advantages of this material over non-genital tissue grafts currently used for urethroplasty (e.g., buccal mucosa) is that the material is "off the shelf." This eliminates the necessity of additional surgical procedures for graft harvesting, which may decrease operative time as well as the potential morbidity from the harvest procedure.

The techniques described above, which employed non-seeded acellular matrices, were successfully applied experimentally and clinically for onlay urethral repairs. However, when tubularized urethral repairs were

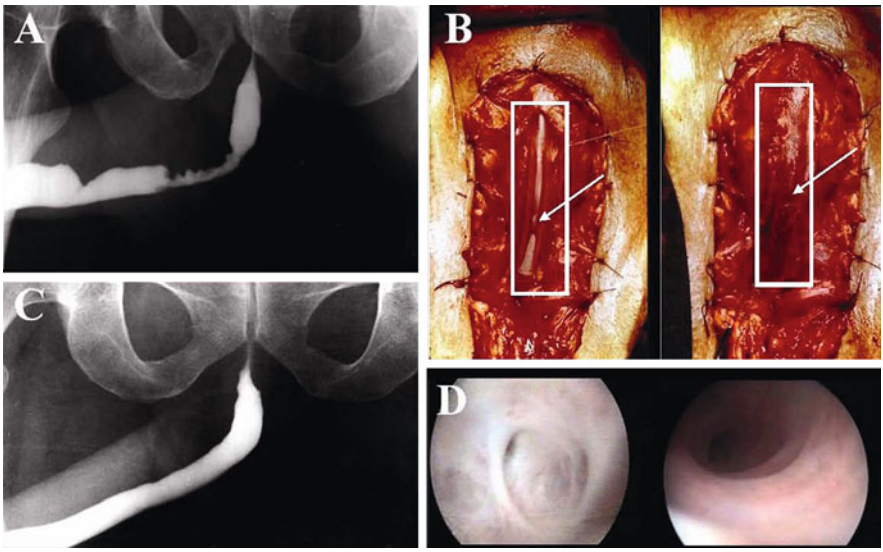

Fig. 16.2. Urethral repair using a collagen matrix. (**a**) Representative case of a patient with a bulbar stricture. (**b**) During surgery, strictured tissue is excised, preserving the urethral plate on the *left side*, and the matrix is anastamosed to the urethral plate in an onlay fashion on the *right*. The boxes in both photos indicate the area of interest, including the urethra, which appears white in the *left* photograph. In the *left* photograph, the *arrow* indicates the area of stricture in the urethra. On the *right*, the *arrow* indicates the repaired stricture. (**c**) Urethrogram 6 months after repair. (**d**) Cystoscopic view of urethra before surgery on the *left* side, and 4 months after repair on the *right* side.

attempted experimentally using these acellular matrices, adequate urethral tissue regeneration was not achieved. Complications, such as graft contracture and stricture formation, ensued (*44*). Tubularized collagen matrices seeded with cells have performed better in animal studies. In a rabbit model, entire urethral segments were resected and urethroplasties were performed with tubularized collagen matrices that were either acellular or seeded with autologous cells. The tubularized collagen matrices seeded with autologous cells formed new tissue which was histologically similar to native urethral tissue (*45*). The tubularized collagen matrices without cells lead to poor tissue development, fibrosis, and stricture formation.

Bladder

Currently, gastrointestinal segments are commonly used for bladder replacement or repair. However, gastrointestinal tissues are designed to absorb the solutes that urinary tissue is designed to excrete, and due to this difference in function, multiple complications can arise, such as infection, metabolic disturbances, urolithiasis, perforation, increased mucus

production, and malignancy (*46–48*). Because of the problems encountered with the use of gastrointestinal segments, numerous investigators have attempted alternative reconstructive procedures for bladder replacement or repair. The use of tissue expansion, seromuscular grafts, and tissue engineering with biomaterial matrices and cell transplantation have been investigated.

Tissue Expansion for Bladder Augmentation

A system of progressive dilation for ureters and bladders has been proposed as a method of bladder augmentation but has not yet been attempted clinically. Augmentation cystoplasty performed with dilated ureteral segments in animals has resulted in an increased bladder capacity ranging from 190 to 380% (*49*, *50*). A system for the progressive expansion of native bladder tissue has also been used for augmenting bladder volumes in animals. Within 30 days after progressive dilation, the neoreservoir volume was expanded at least tenfold. Urodynamic studies showed normal compliance in all animals and microscopic examination of the expanded neoreservoir tissue showed a normal histology. A series of immunocytochemical studies demonstrated that the dilated bladder tissue maintained normal phenotypic characteristics (*50*).

Seromuscular Grafts and De-epithelialized Bowel Segments

Seromuscular grafts and de-epithelialized bowel segments, either alone or over a native urothelium, have also been attempted (*51–56*). Keeping the urothelium intact avoids the complications associated with use of bowel in continuity with the urinary tract (*52*, *53*). An example of this strategy is the combination of the techniques of autoaugmentation with those of enterocystoplasty. An autoaugmentation is performed and the diverticulum is covered with a demucosalized gastric or intestinal segment.

Matrices for Bladder Regeneration

Non-seeded allogeneic acellular matrices have served as scaffolds for the ingrowth of host bladder wall components. The matrices are prepared by mechanically and chemically removing all cellular components from bladder tissue (*5*, *57–59*). The matrices serve as vehicles for partial bladder regeneration, and relevant antigenicity is not evident. One example is SIS, a biodegradable, acellular, xenogeneic collagen-based tissue matrix. SIS was first used in the early 1980s as an acellular matrix for tissue replacement in the vascular field. It has been shown to promote regeneration of a variety of host tissues, including blood vessels and ligaments (*60*). Animal studies

have shown that the non-seeded SIS matrix used for bladder augmentation is able to regenerate in vivo (*61*, *62*).

In multiple studies using various materials as non-seeded grafts for cystoplasty, the urothelial layer was able to regenerate normally, but the muscle layer, although present, was not fully developed (*5*, *57*, *58*, *62*). Often the grafts contracted to 60–70% of their original size with little increase in bladder capacity or compliance (*63*, *64*). Studies involving acellular matrices that may provide the necessary environment to promote cell migration, growth, and differentiation are being conducted. Recently, bladder regeneration has been shown to be more reliable when the SIS was derived from the distal ileum (*61*). With continued research in this area, these matrices may have a clinical role in bladder replacement in the future.

Bladder Replacement Using Tissue Engineering

Cell-seeded allogeneic acellular bladder matrices have been used for bladder augmentation in dogs. A group of experimental dogs underwent a trigone-sparing cystectomy and were randomly assigned to one of three groups. One group underwent closure of the trigone without a reconstructive procedure, another underwent reconstruction with a non-seeded bladder-shaped biodegradable scaffold, and the last underwent reconstruction using a bladder-shaped biodegradable scaffold that was seeded with autologous urothelial and smooth muscle cells (*65*).

The cystectomy-only and non-seeded controls maintained average capacities of 22 and 46% of preoperative values, respectively. However, an average bladder capacity of 95% of the original precystectomy volume was achieved in the cell-seeded tissue engineered bladder replacements. The subtotal cystectomy reservoirs that were not reconstructed and the polymer-only reconstructed bladders showed a marked decrease in bladder compliance (10% and 42% total compliance, respectively). The compliance of the cell-seeded tissue-engineered bladders was almost no different from preoperative values (106%). Histologically, the non-seeded scaffold bladders presented a pattern of normal urothelial cells with a thickened fibrotic submucosa and a thin layer of muscle fibers. The retrieved tissue-engineered bladders showed a normal cellular organization, consisting of a trilayer of urothelium, submucosa, and muscle (*65*).

A clinical experience involving engineered bladder tissue for cystoplasty reconstruction was conducted starting in 1999. A small pilot study of seven patients was reported, using a collagen scaffold seeded with cells either with or without omentum coverage, or a combined PGA-collagen scaffold seeded with cells and omental coverage (see Fig. 16.3). The patients reconstructed with the engineered bladder tissue created with the PGA-collagen cell-seeded scaffolds showed increased compliance, decreased end-filling pressures, increased capacities, and longer dry periods (Fig. 16.4) (*66*).

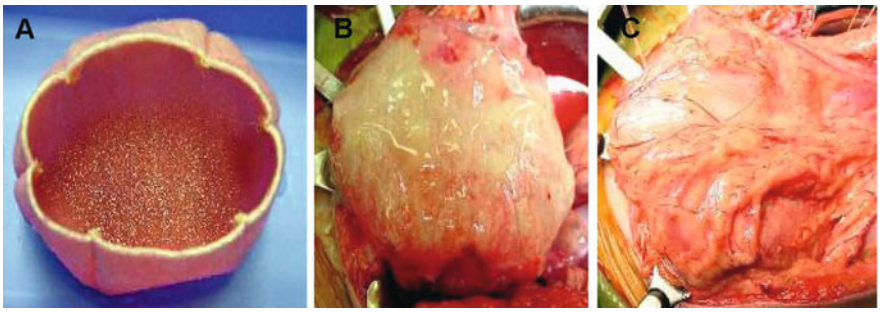

Fig. 16.3. Construction of engineered bladder. (**a**) Scaffold material seeded with cells for use in bladder repair. (**b**) The seeded scaffold is anastamosed to native bladder with running 4-0 polyglycolic sutures. (**c**) Implant covered with fibrin glue and omentum.

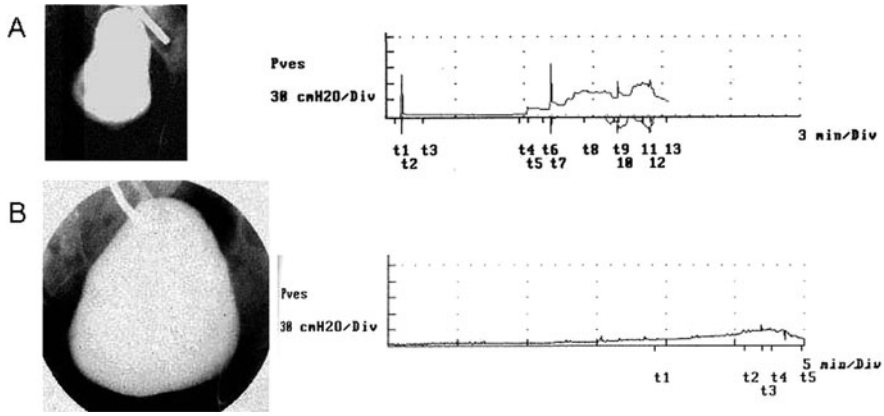

Fig. 16.4. Cystograms and urodynamic studies of a patient before and after implantation of the tissue engineered bladder. (**a**) Preoperative results indicate an irregular bladder in the cystogram and abnormal bladder pressures as the bladder is filled via urodynamic study. (**b**) Postoperatively, findings are significantly improved.

Although the experience is promising in terms of showing that engineered tissues can be implanted safely, it is just a start in terms of accomplishing the goal of engineering fully functional bladders. Further experimental and clinical work is being conducted.

Kidney

The kidney is the most challenging organ in the genitourinary system to reconstruct because of its extremely complex structure and function. Concepts for a bioartificial kidney are currently being explored. Some investigators are pursuing the replacement of isolated kidney function parameters using extracorporeal units, while others are aiming to replace total renal function with tissue-engineered bioartificial renal structures.

Ex Vivo Functioning Renal Units

Dialysis is currently the most common form of renal replacement therapy. However, the relatively high morbidity and mortality resulting from this process have spurred investigators to seek alternative solutions. In an attempt to assess the viability and physiologic functionality of a cell-seeded device to replace the filtration, transport, metabolic, and endocrinologic functions of the kidney, a synthetic hemofiltration device and a device which contained tissue-engineered porcine renal tubules were incorporated into an extracorporeal perfusion circuit, and this was introduced into acutely uremic dogs. Levels of potassium and blood urea nitrogen (BUN) were controlled during treatment with the device. The fractional reabsorption of sodium and water was possible. Active transport of potassium, bicarbonate, and glucose, and a gradual ability to excrete ammonia was observed. These results demonstrated the feasibility of an extracorporeal assist device that is reinforced by the use of proximal tubular cells (*67*).

Using similar techniques, the development of a tissue-engineered bioartificial kidney consisting of a conventional hemofiltration cartridge in series with a renal tubule assist device containing human renal proximal tubule cells was used in patients with acute renal failure in the intensive care unit. The initial clinical experience with this bioartificial kidney suggests that renal tubule cell therapy may provide a dynamic and individualized treatment program as assessed by acute physiologic and biochemical indices (*68*).

Creation of Functional Renal Structures In Vivo

Another approach to improve renal function involves the augmentation of renal tissue with kidney cells expanded in vitro and used for subsequent autologous transplantation. Most recently, an attempt was made to reconstitute renal epithelial cells for the generation of functional nephron units. Renal cells were harvested and expanded in culture. The cells were seeded onto a tubular device constructed from a polycarbonate membrane, which was connected at one end to a Silastic catheter that terminated in a reservoir. The device was implanted in athymic mice. Histologic examination of the implanted devices over time revealed extensive vascularization with formation of glomeruli and highly organized tubule-like structures. Immunocytochemical staining confirmed the renal phenotype. Additionally, yellow fluid was collected from inside the implant, and its creatinine and uric acid concentrations were consistent with the makeup of dilute urine. Further studies have shown the formation of renal structures in cows using cells derived from nuclear transfer protocols. These cells were seeded on a scaffold to form a renal neo-organ similar to those used in the mouse study (Fig. 16.5) (*69*). In addition, the bovine studies investigated the immunocompatibility of these cloned renal cells by measuring how T cells reacted to them in vitro using an EliSPOT assay (Fig. 16.5d). This assay shows that while allogenic

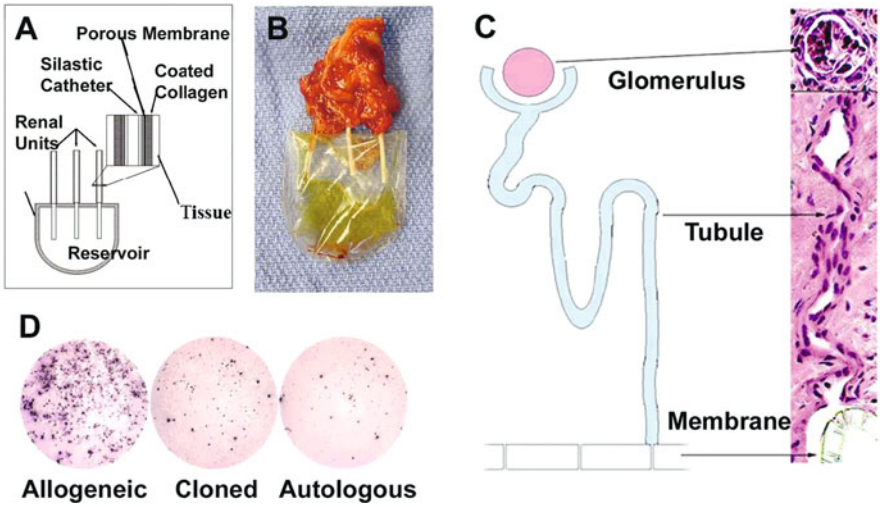

Fig. 16.5. Combining therapeutic cloning and tissue engineering to produce kidney tissue. (**a**) Illustration of the tissue-engineered renal unit. (**b**) Renal unit seeded with cloned cells, three months after implantation, showing the accumulation of urine-like fluid. (**c**) Clear unidirectional continuity between the mature glomeruli, their tubules, and silastic catheter. (**d**) Elispot analyses of the frequencies of T cells that secrete IFNγ after stimulation with allogeneic renal cells, cloned renal cells, or nuclear donor fibroblasts. Cloned renal cells produce fewer IFNγ spots than the allogeneic cells, indicating that the rejection response to cloned cells is diminished. The presented wells are single representatives of duplicate wells.

cells induced interferon γ production in many T cells, which is a sign of rejection, the cloned cells only induced this response in a small number of T cells. In fact, the results with cloned cells were nearly identical to those obtained with the control autologous cells.

This study demonstrated that cells derived from nuclear transfer can be successfully harvested, expanded in culture, and transplanted in vivo with the use of biodegradable scaffolds on which the single suspended cells can organize into tissue structures that are genetically identical to that of the host. This study was also the first demonstration of the use of therapeutic cloning for regeneration of tissues in vivo. The expansion of this system to larger, three-dimensional structures is the next challenge awaiting researchers in the urogenital tissue engineering field.

GENITAL TISSUES

Reconstruction of Corporal Smooth Muscle

One of the major components of the phallus is corporal smooth muscle. The creation of autologous functional and structural corporal tissue de novo would be beneficial in cases of congenital abnormality of the genitals

and in other situations where reconstruction is functionally and aesthetically necessary. To look at the functional parameters of engineered corpora, acellular corporal collagen matrices were obtained from donor rabbit penile tissue, and autologous corpus cavernosal smooth muscle and endothelial cells were harvested, expanded, and seeded on the matrices. The entire rabbit corpora was removed and replaced with the engineered structures. The experimental corporal bodies demonstrated intact structural integrity by cavernosography and showed similar intracoporal pressures by cavernosometry when compared to the normal controls. Rabbits that received scaffolds without cells failed to achieve normal erectile function throughout the study period. However, mating activity in the animals with the cell-seeded corpora appeared normal by one month after implantation. The presence of sperm was confirmed during mating, and was present in all rabbits with the engineered corpora. The female rabbits that mated with the animals implanted with engineered corpora conceived and delivered healthy pups. Animals implanted with the matrix alone were unable to demonstrate normal mating activity and failed to ejaculate into the vagina (*70*, *71*).

Engineered Penile Prostheses

Although silicone is an accepted biomaterial for penile prostheses, biocompatibility is a concern (*72*, *73*). Use of a natural prosthesis composed of autologous cells may be advantageous. In a recent study, the feasibility of applying engineered cartilage rods in situ was investigated (*6*). Autologous chondrocytes were harvested from rabbit ear and expanded in culture. The cells were seeded onto biodegradable poly-L-lactic acid-coated polyglycolic acid polymer rods and then implanted into the corporal spaces of rabbits. Examination at retrieval showed the presence of well-formed, milky-white cartilage structures within the corpora at 1 month and the polymer scaffolding had degraded by two months. There was no evidence of erosion or infection in any of the implantation sites.

Female Genital Tissues

Congenital malformations of the uterus may have profound implications clinically. Patients with cloacal exstrophy and intersex disorders may not have sufficient uterine tissue present for future reproduction. We investigated the possibility of engineering functional uterine tissue using autologous cells. Autologous rabbit uterine smooth muscle and epithelial cells were harvested and expanded in culture. These cells were seeded onto preconfigured uterine-shaped biodegradable polymer scaffolds, and these were used for subtotal uterine tissue replacement in the corresponding autologous animals. Upon retrieval 6 months after implantation, histological, immunocytochemical, and Western blot analyses confirmed the presence of normal

uterine tissue components. Biomechanical analyses and organ bath studies showed that the functional characteristics of these tissues were similar to those of normal uterine tissue. Breeding studies using these engineered uteri are currently being performed.

Similarly, several pathologic conditions, including congenital malformations and malignancy, can adversely affect normal vaginal development or anatomy. To investigate tissue engineering methods of generating vaginal tissue for use in these situations, vaginal epithelial and smooth muscle cells of female rabbits were harvested, grown, and expanded in culture. These cells were seeded onto biodegradable polymer scaffolds, and the cell-seeded constructs were then implanted into nude mice for up to 6 weeks. Immunocytochemical, histological, and Western blot analyses confirmed the presence of vaginal tissue phenotypes. Electrical field stimulation studies in the tissue-engineered constructs showed similar functional properties to those of normal vaginal tissue. When these constructs were used for autologous total vaginal replacement, patent vaginal structures were noted in the tissue-engineered specimens, while the non-cell-seeded structures were noted to be stenotic (*74*).

Injectable Therapies

Both urinary incontinence and vesicoureteral reflux are common conditions affecting the pediatric genitourinary system. Currently, injectable bulking agents are one treatment used clinically for these conditions, but biocompatibility of current synthetic bulking agents is a concern. The ideal substance for endoscopic treatment of reflux and incontinence should be injectable, non-antigenic, non-migratory, volume stable, and safe for human use. Animal studies have shown that chondrocytes (cartilage cells) can be easily harvested and combined with alginate in vitro and the resulting suspension can be easily injected cystoscopically. The elastic cartilage tissue formed as a result of the injection is able to correct vesicoureteral reflux without any evidence of obstruction. This technology has been applied in humans for the correction of vesicoureteral reflux in children (Fig. 16.6) and for urinary incontinence in adults (*75*, *76*).

Using cell therapy techniques, the use of autologous smooth muscle cells has been explored for both urinary incontinence and vesicoureteral reflux applications. The potential use of injectable, cultured myoblasts for the treatment of stress urinary incontinence has also been investigated (*77*, *78*). The use of injectable muscle precursor cells has also been investigated for use in the treatment of urinary incontinence due to irreversible urethral sphincter injury or maldevelopment (*79*). A clinical trial involving the use of muscle derived stem cells (MDSC) to treat stress urinary incontinence has also been performed with good results. Biopsies of skeletal muscle were obtained and autologous myoblasts and fibroblasts were cultured. Under ultrasound guidance, myoblasts were injected into the rhabdosphincter and fibroblasts

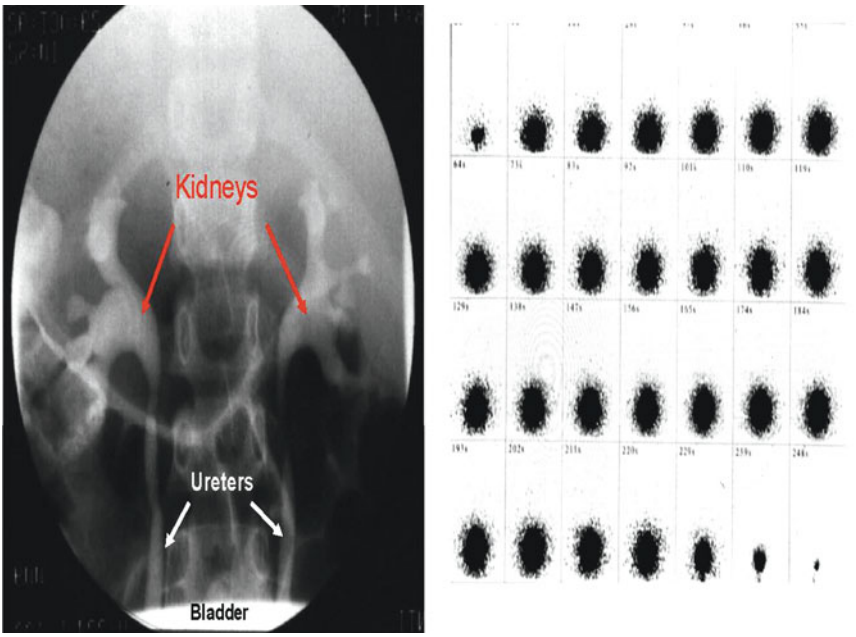

Fig. 16.6. Autologous chondrocytes for the treatment of vesicoureteral reflux. (**a**) Preoperative voiding cystourethrogram of a patient with bilateral reflux. Here, contrast material can be seen within both ureters and within the kidneys, indicating reflux is present. (**b**) Postoperative radionuclide cystogram of the same patient 6 months after injection of autologous chondrocytes.

mixed with collagen were injected into the submucosa. One year following injection, the thickness and function of the rhabdosphincter had significantly increased, and all patients were continent (*80*). These are the first demonstrations of the replacement of both sphincter muscle tissue and its innervation by the injection of muscle precursor cells. In addition, injectable muscle-based gene therapy and tissue engineering were combined to improve detrusor function in a bladder injury model, and may potentially be a novel treatment option for urinary incontinence (*81*).

Patients with testicular dysfunction require androgen replacement for somatic development. Conventional treatment for testicular dysfunction consists of periodic intramuscular injections of chemically modified testosterone or application of a transdermal testosterone patch. However, long-term non-pulsatile testosterone therapy is not optimal and can cause multiple problems, including erythropoiesis and bone density changes.

A system was designed wherein Leydig cells were microencapsulated for controlled testosterone replacement. Purified Leydig cells were isolated and encapsulated in an alginate-poly-L-lysine solution. The encapsulated Leydig cells were injected into castrated animals, and serum testosterone was measured serially; the animals were able to maintain testosterone levels in

the long term (*82*). These studies suggest that microencapsulated Leydig cells may be able to replace or supplement testosterone in situations where anorchia or testicular failure is present.

CONCLUSION

Tissue engineering efforts are currently being undertaken for every type of tissue and organ within the urinary system. Most of the effort expended to engineer genitourinary tissues has occurred within the last decade. While some tissue engineering applications are beginning to enter clinical practice, many of the new tissue engineering techniques described must be studied further before they can be applied to human disorders. However, recent progress suggests that engineered urologic tissues and cell therapy may have clinical applicability, particularly in reconstruction of this system in children.

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REFERENCES

1. Hynes RO. Integrins: versatility, modulation, and signaling in cell adhesion. Cell 1992;69:11–25.
2. Kim BS, Mooney DJ. Development of biocompatible synthetic extracellular matrices for tissue engineering. Trends Biotechnol 1998;16:224–30.
3. Pariente JL, Kim BS, Atala A. In vitro biocompatibility assessment of naturally derived and synthetic biomaterials using normal human urothelial cells. J Biomed Mater Res 2001;55:33–9.
4. Pariente JL, Kim BS, Atala A. In vitro biocompatibility evaluation of naturally derived and synthetic biomaterials using normal human bladder smooth muscle cells. J Urol 2002;167:1867–71.
5. Yoo JJ, Meng J, Oberpenning F, Atala A. Bladder augmentation using allogenic bladder submucosa seeded with cells. Urology 1998;51:221–5.
6. Yoo JJ, Park HJ, Lee I, Atala A. Autologous engineered cartilage rods for penile reconstruction. J Urol 1999;162:1119–21.
7. Amiel GE, Komura M, Shapira O, et al. Engineering of blood vessels from acellular collagen matrices coated with human endothelial cells. Tissue Eng 2006;12:2355–65.
8. Atala A. Engineering tissues and organs. Curr Opin Urol 1999;9:517–26.
9. Atala A. Autologous cell transplantation for urologic reconstruction. J Urol 1998;159: 2–3.
10. Atala A. Tissue engineering and regenerative medicine: concepts for clinical application. Rejuvenation Res 2004;7:15–31.
11. Lin HK, Cowan R, Moore P, et al. Characterization of neuropathic bladder smooth muscle cells in culture. J Urol 2004;171:1348–52.
12. Lai JY, Yoon CY, Yoo JJ, Wulf T, Atala A. Phenotypic and functional characterization of in vivo tissue engineered smooth muscle from normal and pathological bladders. J Urol 2002;168:1853–7; discussion 8.

13. Cilento BG, Freeman MR, Schneck FX, Retik AB, Atala A. Phenotypic and cytogenetic characterization of human bladder urothelia expanded in vitro. J Urol 1994;152: 665–70.
14. Scriven SD, Booth C, Thomas DF, Trejdosiewicz LK, Southgate J. Reconstitution of human urothelium from monolayer cultures. J Urol 1997;158:1147–52.
15. Liebert M, Hubbel A, Chung M, et al. Expression of mal is associated with urothelial differentiation in vitro: identification by differential display reverse-transcriptase polymerase chain reaction. Differentiation 1997;61:177–85.
16. Puthenveettil JA, Burger MS, Reznikoff CA. Replicative senescence in human uroepithelial cells. Adv Exp Med Biol 1999;462:83–91.
17. Freeman MR, Yoo JJ, Raab G, et al. Heparin-binding EGF-like growth factor is an autocrine growth factor for human urothelial cells and is synthesized by epithelial and smooth muscle cells in the human bladder. J Clin Invest 1997;99:1028–36.
18. Nguyen HT, Park JM, Peters CA, et al. Cell-specific activation of the HB-EGF and ErbB1 genes by stretch in primary human bladder cells. In Vitro Cell Dev Biol Anim 1999;35:371–5.
19. Liebert M, Wedemeyer G, Abruzzo LV, et al. Stimulated urothelial cells produce cytokines and express an activated cell surface antigenic phenotype. Semin Urol 1991;9:124–30.
20. Brivanlou AH, Gage FH, Jaenisch R, Jessell T, Melton D, Rossant J. Stem cells. Setting standards for human embryonic stem cells. [see comment]. Science 2003;300:913–6.
21. Reubinoff BE, Pera MF, Fong CY, Trounson A, Bongso A. Embryonic stem cell lines from human blastocysts: somatic differentiation in vitro.[see comment][erratum appears in Nat Biotechnol 2000 May;18(5):559]. Nat Biotechnol 2000;18:399–404.
22. Thomson JA, Itskovitz-Eldor J, Shapiro SS, et al. Embryonic stem cell lines derived from human blastocysts.[see comment][erratum appears in Science 1998 Dec 4;282(5395):1827]. Science 1998;282:1145–7.
23. Reubinoff BE, Itsykson P, Turetsky T, et al. Neural progenitors from human embryonic stem cells.[see comment]. Nat Biotechnol 2001;19:1134–40.
24. Schuldiner M, Eiges R, Eden A, et al. Induced neuronal differentiation of human embryonic stem cells. Brain Res 2001;913:201–5.
25. Schuldiner M, Yanuka O, Itskovitz-Eldor J, Melton DA, Benvenisty N. Effects of eight growth factors on the differentiation of cells derived from human embryonic stem cells. Proc Natl Acad Sci USA 2000;97:11307–12.
26. Kaufman DS, Hanson ET, Lewis RL, Auerbach R, Thomson JA. Hematopoietic colony-forming cells derived from human embryonic stem cells. Proc Natl Acad Sci USA 2001;98:10716–21.
27. Kehat I, Kenyagin-Karsenti D, Snir M, et al. Human embryonic stem cells can differentiate into myocytes with structural and functional properties of cardiomyocytes.[see comment]. J Clin Invest 2001;108:407–14.
28. Levenberg S, Golub JS, Amit M, Itskovitz-Eldor J, Langer R. Endothelial cells derived from human embryonic stem cells. Proc Natl Acad Sci USA 2002;99:4391–6.
29. Assady S, Maor G, Amit M, Itskovitz-Eldor J, Skorecki KL, Tzukerman M. Insulin production by human embryonic stem cells. Diabetes 2001;50:1691–7.
30. Delo DM, De Coppi P, Bartsch G, Jr., Atala A. Amniotic fluid and placental stem cells. Methods Enzymol 2006;419:426–38.
31. De Coppi P, Bartsch G, Jr., Siddiqui MM, et al. Isolation of amniotic stem cell lines with potential for therapy.[see comment]. Nat Biotechnol 2007;25:100–6.
32. Guillot PV, O'Donoghue K, Kurata H, Fisk NM. Fetal stem cells: betwixt and between. Sem Reprod Med 2006;24:340–7.
33. Broxmeyer HE, Srour E, Orschell C, et al. Cord blood stem and progenitor cells. Methods Enzymol 2006;419:439–73.
34. Burke ZD, Thowfeequ S, Peran M, Tosh D. Stem cells in the adult pancreas and liver. Biochem J 2007;404:169–78.
35. Nern C, Momma S. The realized niche of adult neural stem cells. Stem Cell Reviews 2006;2:233–40.

36. Wilmut I, Schnieke AE, McWhir J, Kind AJ, Campbell KH. Viable offspring derived from fetal and adult mammalian cells.[see comment][erratum appears in Nature 1997 Mar 13;386(6621):200]. Nature 1997;385:810–3.
37. Hochedlinger K, Rideout WM, Kyba M, Daley GQ, Blelloch R, Jaenisch R. Nuclear transplantation, embryonic stem cells and the potential for cell therapy. Hematol J 2004;5 Suppl 3:S114–7.
38. Olsen L, Bowald S, Busch C, Carlsten J, Eriksson I. Urethral reconstruction with a new synthetic absorbable device. An experimental study. Scand J Urol Nephrol 1992;26: 323–6.
39. Atala A, Vacanti JP, Peters CA, Mandell J, Retik AB, Freeman MR. Formation of urothelial structures in vivo from dissociated cells attached to biodegradable polymer scaffolds in vitro. J Urol 1992;148:658–62.
40. Kropp BP, Ludlow JK, Spicer D, et al. Rabbit urethral regeneration using small intestinal submucosa onlay grafts. Urology 1998;52:138–42.
41. Sievert KD, Bakircioglu ME, Nunes L, Tu R, Dahiya R, Tanagho EA. Homologous acellular matrix graft for urethral reconstruction in the rabbit: histological and functional evaluation. J Urol 2000;163:1958–65.
42. Atala A, Guzman L, Retik AB. A novel inert collagen matrix for hypospadias repair. J Urol 1999;162:1148–51.
43. Chen F, Yoo JJ, Atala A. Acellular collagen matrix as a possible "off the shelf" biomaterial for urethral repair. Urology 1999;54:407–10.
44. le Roux PJ. Endoscopic urethroplasty with unseeded small intestinal submucosa collagen matrix grafts: a pilot study. J Urol 2005;173:140–3.
45. Roger EDF, James JY, Anthony A. Urethral replacement using cell seeded tubularized collagen matrices. J Urol 2002;168:1789–93.
46. McDougal WS. Metabolic complications of urinary intestinal diversion. J Urol 1992;147:1199–208.
47. Kaefer M, Hendren WH, Bauer SB, et al. Reservoir calculi: a comparison of reservoirs constructed from stomach and other enteric segments.[see comment]. J Urol 1998;160:2187–90.
48. Kaefer M, Tobin MS, Hendren WH, et al. Continent urinary diversion: the Children's Hospital experience. J Urol 1997;157:1394–9.
49. Lailas NG, Cilento B, Atala A. Progressive ureteral dilation for subsequent ureterocystoplasty. J Urol 1996;156:1151–3.
50. Satar N, Yoo JJ, Atala A. Progressive dilation for bladder tissue expansion. J Urol 1999;162:829–31.
51. Blandy JP. Ileal pouch with transitional epithelium and anal sphincter as a continent urinary reservoir. J Urol 1961;86:749–67.
52. Blandy JP. The feasibility of preparing an ideal substitute for the urinary bladder. Ann R Coll Surg Engl 1964;35:287–311.
53. Harada N, Yano H, Ohkawa T, Misse T, Kurita T, Nagahara A. New surgical treatment of bladder tumours: mucosal denudation of the bladder. Br J Urol 1965;37:545–7.
54. Oesch I. Neourothelium in bladder augmentation. An experimental study in rats. Eur Urol 1988;14:328–9.
55. Salle JL, Fraga JC, Lucib A, et al. Seromuscular enterocystoplasty in dogs. J Urol 1990;144:454–6; discussion 60.
56. Cheng E, Rento R, Grayhack JT, Oyasu R, McVary KT. Reversed seromuscular flaps in the urinary tract in dogs. J Urol 1994;152:2252–7.
57. Probst M, Dahiya R, Carrier S, Tanagho EA. Reproduction of functional smooth muscle tissue and partial bladder replacement. Br J Urol 1997;79:505–15.
58. Sutherland RS, Baskin LS, Hayward SW, Cunha GR. Regeneration of bladder urothelium, smooth muscle, blood vessels and nerves into an acellular tissue matrix. J Urol 1996;156:571–7.
59. Piechota HJ, Dahms SE, Nunes LS, Dahiya R, Lue TF, Tanagho EA. In vitro functional properties of the rat bladder regenerated by the bladder acellular matrix graft. J Urol 1998;159:1717–24.

60. Badylak SF, Lantz GC, Coffey A, Geddes LA. Small intestinal submucosa as a large diameter vascular graft in the dog. J Surg Res 1989;47:74–80.
61. Kropp BP, Cheng EY, Lin HK, Zhang Y. Reliable and reproducible bladder regeneration using unseeded distal small intestinal submucosa. J Urol 2004;172:1710–3.
62. Kropp BP, Rippy MK, Badylak SF, et al. Regenerative urinary bladder augmentation using small intestinal submucosa: urodynamic and histopathologic assessment in long-term canine bladder augmentations. J Urol 1996;155:2098–104.
63. Portis AJ, Elbahnasy AM, Shalhav AL, et al. Laparoscopic augmentation cystoplasty with different biodegradable grafts in an animal model. J Urol 2000;164:1405–11.
64. Landman J, Olweny E, Sundaram CP, et al. Laparoscopic mid sagittal hemicystectomy and bladder reconstruction with small intestinal submucosa and reimplantation of ureter into small intestinal submucosa: 1-year followup. J Urol 2004;171:2450–5.
65. Oberpenning F, Meng J, Yoo JJ, Atala A. De novo reconstitution of a functional mammalian urinary bladder by tissue engineering.[see comment]. Nat Biotechnol 1999;17:149–55.
66. Atala A, Bauer SB, Soker S, Yoo JJ, Retik AB. Tissue-engineered autologous bladders for patients needing cystoplasty. Lancet 2006;367:1241–6.
67. Humes HD, Buffington DA, MacKay SM, Funke AJ, Weitzel WF. Replacement of renal function in uremic animals with a tissue-engineered kidney.[see comment]. Nat Biotechnol 1999;17:451–5.
68. Humes HD, Weitzel WF, Bartlett RH, Swaniker FC, Paganini EP. Renal cell therapy is associated with dynamic and individualized responses in patients with acute renal failure. Blood Purif 2003;21:64–71.
69. Lanza RP, Chung HY, Yoo JJ, et al. Generation of histocompatible tissues using nuclear transplantation.[see comment]. Nat Biotechnol 2002;20:689–96.
70. Yoo JJ, Park HJ, Atala A. Tissue-engineering applications for phallic reconstruction. World J Urol 2000;18:62–6.
71. Yoo JJ, Atala A. Tissue engineering of genitourinary organs. Ernst Schering Research Foundation Workshop 2002:105–27.
72. Nukui F, Okamoto S, Nagata M, Kurokawa J, Fukui J. Complications and reimplantation of penile implants. Int J Urol 1997;4:52–4.
73. Thomalla JV, Thompson ST, Rowland RG, Mulcahy JJ. Infectious complications of penile prosthetic implants. J Urol 1987;138:65–7.
74. De Filippo RE, Yoo JJ, Atala A. Engineering of vaginal tissue in vivo. Tissue Eng 2003;9:301–6.
75. Diamond DA, Caldamone AA. Endoscopic correction of vesicoureteral reflux in children using autologous chondrocytes: preliminary results. J Urol 1999;162:1185–8.
76. Bent AE, Tutrone RT, McLennan MT, Lloyd LK, Kennelly MJ, Badlani G. Treatment of intrinsic sphincter deficiency using autologous ear chondrocytes as a bulking agent. Neurourol Urodyn 2001;20:157–65.
77. Yokoyama T, Huard J, Chancellor MB. Myoblast therapy for stress urinary incontinence and bladder dysfunction. World J Urol 2000;18:56–61.
78. Chancellor MB, Yokoyama T, Tirney S, et al. Preliminary results of myoblast injection into the urethra and bladder wall: a possible method for the treatment of stress urinary incontinence and impaired detrusor contractility. Neurourol Urodyn 2000;19:279–87.
79. Yiou R, Yoo JJ, Atala A. Restoration of functional motor units in a rat model of sphincter injury by muscle precursor cell autografts. Transplantation 2003;76:1053–60.
80. Strasser H, Berjukow S, Marksteiner R, et al. Stem cell therapy for urinary stress incontinence. Exp Gerontol 2004;39:1259–65.
81. Huard J, Yokoyama T, Pruchnic R, et al. Muscle-derived cell-mediated ex vivo gene therapy for urological dysfunction. Gene Ther 2002;9:1617–26.
82. Machluf M, Orsola A, Boorjian S, Kershen R, Atala A. Microencapsulation of Leydig cells: a system for testosterone supplementation. Endocrinology 2003;144:4975–9.

IV Miscellaneous Topics

17 Adolescent Urology

Christopher Woodhouse

Abstract The rarity of the major congenital anomalies of the genito-urinary tract and the idiosyncrasies of adolescents make the management difficult for the general urologist. The necessary steps include: 1. Arrangement of transitional care so that the child and the family are comfortable with the adult urologist before completely leaving the pediatric environment. 2. Establishment of the specific needs and goals of the patient. 3. Gradual transfer of responsibility from the parents to the new adult patient. 4. Identification of relevant specialists to share care. 5. Management of renal, bladder and sexual problems.

Keywords Urology · Adolescence · Transition · Congenital anomalies

INTRODUCTION

The passage from childhood to adult life is usually rather traumatic. Chronic illness can magnify the problems and create new ones. Adolescent medicine is rapidly becoming a subject in its own right and sub-specialist areas are developing.

There are two parts to such care:

1. Management of the emotional and physical changes that occur in the adolescent period.
2. The medical care both in adolescence and throughout adult life.

The first is common to virtually all adolescent sub-specialties. The second depends on whether there is an adult equivalent of the pediatric condition.

A child with insulin-dependent diabetes, for example, needs special care in adolescence but may then be looked after in an adult clinic. Most of the genito-urinary anomalies have no adult equivalent. There is no adult equivalent of exstrophy, posterior urethral valves, ano-rectal agenesis or disorders of gender identity. Even spina bifida is not the same as acquired spinal cord injury.

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An adult urologist who takes on the care of an adolescent with one of the major conditions discussed elsewhere in this book will find that adult urological training has provided little help. The patient will need special care continued for life. As with so many complex problems, the care involves several disciplines with urological co-ordination. It would be usual to have close links with nephrology, gynecology, psychology, imaging and gastroenterology.

TRANSITIONAL CARE

Although children have a natural wish to break away from home as they become teenagers, those who have been very dependent on the total care provided by a pediatric hospital may be frightened by the great step of moving to the adult hospital at whatever age it is suggested. This will be particularly true if there is no pathway of transitional care and no adult urologist who understands the long-term problems of the major congenital and acquired anomalies of the child's genito-urinary tract.

In the absence of a formal system of transitional care, the adult urologist must start by establishing the status of the whole urinary tract. Sometimes, even the diagnosis will have been lost in the mists of time!

Unless the kidneys are completely normal, the following tests should be done:

1. Measurement of glomerular filtration rate.
2. Differential function on isotope scan.
3. Measurement of blood pressure.
4. Measurement of urinary protein.

For the lower urinary tract, the information may be quite simple. However, children who have had major reconstructions will have a complex anatomy which may even have been changed on two or three occasions. The following should be known:

1. Of what tissues is the urinary reservoir constructed.
2. How is it emptied.
3. What is the condition of the remaining intestine.
4. What is the pattern of infections.
5. Are there resultant metabolic problems such as hyperchloraemic acidosis or vitamin B_{12} deficiency.

The genital tract, especially in girls, may not have been much investigated in childhood. Often there has been a laparotomy in infancy but the condition of the internal genitalia not have been recorded or even recorded wrongly. It may take a careful search of the records to find if the uterus, tubes and ovaries were normal.

It is particularly important in boys with a missing scrotal testis to note where it is thought to be (this may save a futile search for one that has actu-

ally been removed, or prompt a search for an intra-abdominal one which may become malignant).

Patients born with disorders of sexual development (DSD, formerly known as intersex conditions) need very special care. In the past, there was a widespread practice to decide on a sex of rearing and stick to it without the child ever being aware of the original diagnostic dilemma. Although this practice has largely been abandoned in favour of a more conservative approach with the involvement of the family and, later, with the child, there are still patients reaching adult life without disclosure of the diagnosis or genetic status. It is essential that adolescents with DSD are cared for by a multidisciplinary group with specialised knowledge of these rare conditions.

It is also important to note that even if disclosure of diagnosis in DSD (and all other conditions) has been made children may not have understood and knowledge may not have been updated as they matured. When I see new patients in the adolescent clinic, I usually ask what they think is their diagnosis; it is seldom that one will have any idea of the answer! This is not through secrecy on the part of doctors or parents, but a failure to realise that information is not passively absorbed by the child.

A particularly difficult aspect of transitional care is the establishment of the patient as the decision-maker. In childhood, decisions are made by the parents in discussion with the physician. The child is increasingly involved with maturity, but it is a rare family that gives the total care to the child. In adolescence, two changes occur, usually simultaneously. First, the patient wishes to break away from the parents and start to make decisions alone. Second, there is a change in priorities so that the adolescent sees requirements that the parents do not consider important and vice versa.

The new medical team have a difficult tight rope on which to walk! It is most important for the new physician to remember who is now the patient and not become a go-between in a parent/adolescent battle. A common problem arises when a non-life threatening symptom, for example, poor urinary continence, is seen by the parents as devastating and by the adolescent as unimportant.

In most societies, even when patients have not reached the legal age of consent, they are deemed competent to make medical decisions providing they understand the consequences of their actions (in the UK this is called Gillick competence after the legal case that established the precedent).

A more difficult, but fortunately rare problem arises when an adolescent refuses life-saving treatment. Such cases will always require involvement of mental health teams and often legal ones as well.

There is no easy way of transferring responsibility from parents to the adolescent. A good start can be made when the pediatric team first introduce the family to the adult urologist. I find it helpful, right from the start, to converse directly with the patient. Even when the parents ask a question, I prefer to address the answer to the patient. There will usually be an opportunity to examine the patient and the parents can be asked to wait outside.

The physician can then ask if there are any private concerns that need discussion.

Most patients want to discuss their sexuality but are afraid to ask. Most physicians are afraid that they will ask! It is not usually a good idea for the physician to ask outright if sex is on the agenda. If the patient (or parents) broach the subject, it must be addressed in a truthful and straight forward manner. Some families will have been given unrealistic expectations. If it is not raised at the first meeting, the subject must be introduced gently and sensitively in the subsequent ones.

During transition, the other specialties that will be needed can be identified. Just as the urological requirements are complex, so are those of nephrology, psychology, orthopaedics and gynecology. Without an enthusiastic team, adolescent care will be difficult.

Transitional care box

- Plan the transfer to adult care in good time
- Introduce child and parents to the adult team
- Establish the anatomy and physiology of the genito-urinary tract
- Ask the child what he/she thinks is the diagnosis
- Begin the transfer of responsibility for decisions to the patient
- Enable the discussion of sexuality
- Identify supporting specialists

THE KIDNEYS

Renal Function

Damage to the kidneys occurs in foetal life in many of the congenital urological anomalies. Although the structural anomaly, such as a posterior urethral valve, may be corrected just after birth (or even in utero) the kidneys may never recover so that hypertension and renal failure develop in later life. Renal follow-up is an integral part of adolescent care. Blood pressure measurement, tests for urinary protein and serum creatinine must be a part of the annual review. The most useful guide for the long-term monitoring of proteinuria is the protein/creatinine ratio.

Patients who reach adolescence with a glomerular filtration rate (GFR) of less than 40 ml/min/1.73 m^2 have a substantial chance of developing end stage renal failure within 16 years (Fig. 17.1) (*1*). The downward progress can be slowed with rigorous control of proteinuria and blood pressure with angiotensin conversion enzyme inhibitors (ACEI).

The cause is probably hyperperfusion injury of surviving nephrons, but a watch must be kept for continuing damage to the kidneys by the bladder especially in boys born with posterior urethral valves.

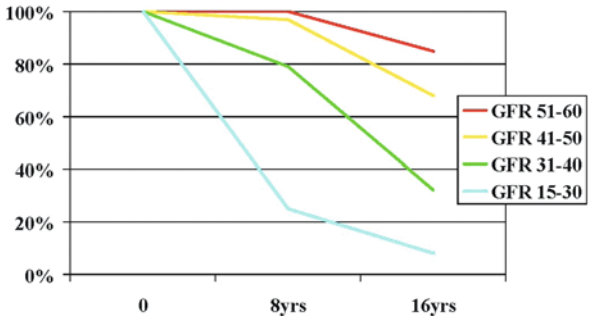

Fig. 17.1. Percentage of patients surviving *without* dialysis/transplantation by initial GFR corrected to 1.73 m^2. Time zero was at entry into adolescent follow-up around puberty (*1*).

Hypertension

Damaged kidneys cause hypertension. Even a small scar may be incriminated. If scars are suspected, a DMSA scan is essential (Fig. 17.2). All patients must have the blood pressure measured once a year.

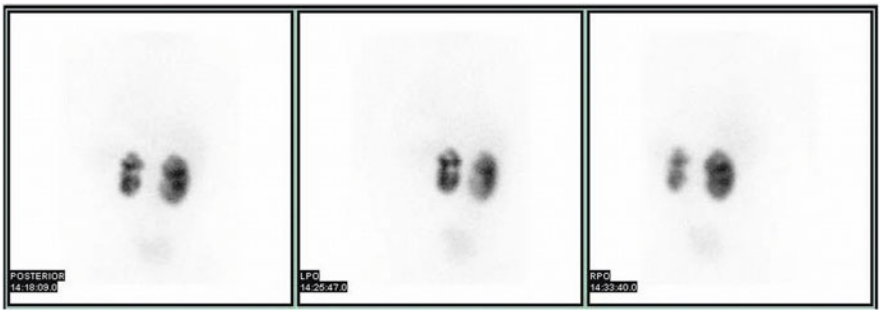

Fig. 17.2. Tc-99m DMSA scan showing bilateral cortical scarring. The changes are more profound on the left side compared to right. The left kidney contributes 37% to total renal function; right 63%. (Courtesy of Dr J.Bomanji.)

The risk of hypertension has been best documented in patients with reflux nephropathy. In assessing risk, however, it is essential to remember that normal blood pressure increases with age (Fig. 17.3). The traditional cut-off for normality of 140/90 mmHg is not appropriate for adolescents.

The range given in the literature for the incidence of hypertension is very wide, partly from the definition used and partly from the inclusion criteria of the study. The risk certainly increases with age. It seems likely that a patient with unilateral nephropathy 18 years old has a 12% risk of hypertension (*2*). At the top end, a 27 year old with bilateral nephropathy may have a risk as high as 44% (*3*). More conservative figures of 18.5% and even 12% were given by Wallace et al. and Smellie et al., respectively (*4*, *5*).

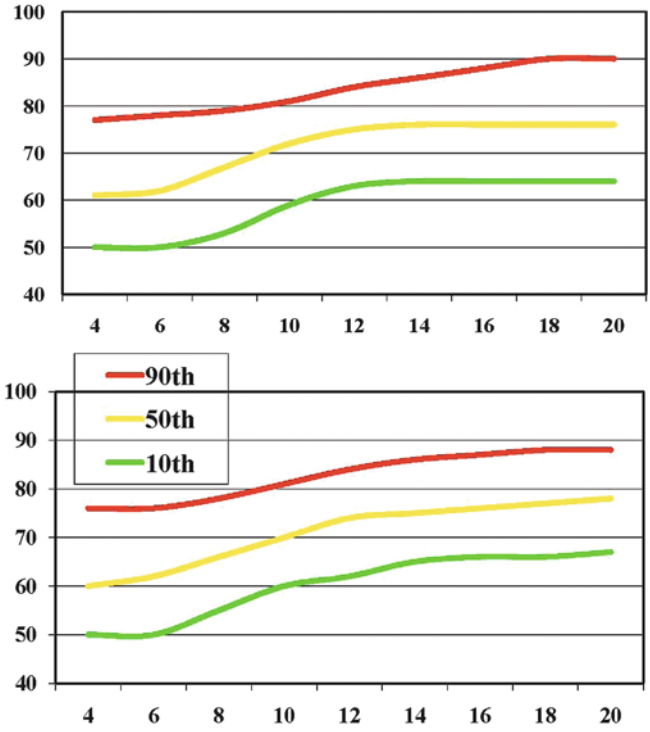

Fig. 17.3. Diastolic blood pressure by age in boys (*upper graph*) and girls (*lower graph*) (25).

The kidney box

- Establish the blood pressure and renal function at the first visit
- Damaged kidneys may cause hypertension. The blood pressure must be measured at least annually, remembering the age adjusted norms
- Patients with a glomerular filtration rate below 40 ml/min/1.73m2 have a substantial risk of end stage renal failure.
- Creatinine and urine protein should be measured at least annually
- Although deteriorating renal function is usually due to hyper filtration injury, anatomical or functional problems in the lower urinary tract should also be considered as a cause.
- Enlist the help of a nephrologist.

THE BLADDER OR URINARY RESERVOIR

Classically, the bladder is described as an organ for the storage and evacuation of urine. However, at all ages, but particularly in the young, the

function of the bladder may have a profound effect on renal function. The monitoring of the one cannot be separated from that of the other.

Posterior Urethral Valves

It is essential to understand that the main long-term consequences of posterior urethral valves (PUV) occur because of damage to the bladder by obstructed voiding in utero and in the neonatal period before the valve is resected. They consist of loss of compliance, detrusor instability and reduced functional capacity. In adulthood, the pattern may change to one of chronic retention, often with high pressure.

Although not seen in all PUV boys, the potential for such damage is always present and may not be manifest until adolescence or early adult life. The symptoms will be familiar to all urologists as frequency, urgency and incontinence. What may not be recognised is the relentless effect on the kidney.

The progressive nature of renal failure in PUV boys has been recognised for many years. In 1988 the incidence of renal failure was 23% at 10 years old (yo), 30% at 16 yo and 43% at 30 yo (*6*). In spite of a greater understanding of the pathophysiology of the valve bladder, these figures have not greatly improved (18%, 32 and 36%, respectively, in 2005) (*7*). A normal serum creatinine at the beginning of puberty does not mean that it will be normal at the end.

Apart from the renal damage caused by the unrelieved obstruction before the valve resection, there is ongoing damage from the poorly compliant bladder. Upper tract obstruction causes damage to the renal medulla resulting in concentration defects and polyuria. There are, therefore, more bladder filling cycles in a day so that longer periods are spent with dangerously high bladder storage pressures, thus further worsening renal damage. Factors of poor prognostic significance are diagnosis before the age of 1 (including intra uterine diagnosis), diurnal incontinence after 5 yo, persistent bilateral reflux and polyuria (*6*). There is a suggestion from recent work that renal failure may be prevented by aggressive bladder management with anticholinergics, self-catheterisation and clam cystoplasty (*8*).

The valve bladder box

- Irreversible damage to the bladder and kidneys occurs in utero
- The incidence of end stage renal failure at 30 yo is about 35%
- A normal creatinine at the onset of puberty does not mean that it will be normal in adulthood
- In adolescence, the bladder may deteriorate, developing high pressure chronic retention
- Monitoring of renal function, proteinuria and residual urine must be done at least annually

Exstrophy

Children with exstrophy have an isolated anomaly and generally grow up very well. The reconstructed bladder may not be durable into adulthood. Only 23% of exstrophy children who are now adults avoided a diversion. Of those whose bladder reconstruction survives childhood, up to 60% will require further reconstruction in adolescence or early adult life (*9*).

In children born in the last 20 years, the results of reconstruction, with or without augmentation have been much better. It is generally done in first day or so of life. It is reasonable to expect that the results will be more durable.

If the bladder does deteriorate in early adult life, the investigation should be along standard lines with imaging and urodynamic studies. There is a particular difficulty when the child leaves school. In a disciplined environment a bladder that has a 'dry interval' of about 3–4 h may appear to be continent. With the more haphazard life of work or college, it may not be convenient to void by the clock and the patient may become incontinent – the bladder has not changed, but the way of life has.

If the bladder as a reservoir is inadequate through high pressure or low capacity, it should be augmented using standard surgical techniques.

The bladder outlet is much more of a problem. There are no natural sphincters. If the bladder is enlarged, the outlet may become continent. However, emptying may no longer be possible and clean intermittent self catheterisation (CIC) may be necessary. The reconstructed urethra may not be easy to catheterise and a check should always be made before surgery.

If the outlet is too weak, a further bladder neck reconstruction may be possible but the results are not good. It may be better to close the bladder neck and form a Mitrofanoff channel for CIC.

The bladder in exstrophy is at risk of developing cancer at a young age. The incidence is 645 times that of the normal population by the age of 40 years. Most cases have been described in those who were diverted in childhood, leaving part or all, of the bladder defunctioned (Fig. 17.4). It is possible that the risk will be lower with a functioning bladder (*10*).

The exstrophy bladder box

- In exstrophy, a bladder that is continent and empties completely in childhood may not continue to do so in adult life.
- Bladder function must be monitored at least annually by ultra-sound
- At least in patients who have a urinary diversion, the risk of cancer in the bladder remnant is very high. The risk with a functioning bladder is unknown

Fig. 17.4. Clinical photograph of a man born with exstrophy with a carcinoma of the bladder ulcerating through the open urethra.

Intestinal Urinary Reservoirs

All urinary reservoirs made of intestine have the same basic long-term problems. Hyperchloraemic acidosis occurs in up to 14% of patients though many more may have a metabolic acidosis with respiratory compensation. Anaemia occurs in 8% (*11*). Vitamin B_{12} deficiency is a risk after 5 years especially if terminal ileum is used (*12*).

Reservoir stones occur in 12–15% of patients. Risk factors include infection, need for CIC and retained mucus. Recent work has suggested that there may be metabolic abnormalities in some patients with enterocystoplasty that predispose to stone formation. The most important are low urinary citrate and high pH (*13*)

A particular worry is the possibility of abnormalities in bone development in children. Growth in height and weight are normal (*14*). In rats with ureterosigmoidostomies there is loss of development of the femora unless continuous antibiotics are given (*15*). In all forms of enterocystoplasty there is significant loss of bone mineral density due to expansion of marrow cavity regardless of antibiotic administration (*16*). Resolution of this problem is of particular importance especially with the renewed enthusiasm for modified forms of ureterosigmoidostomy such as the Mainz II. However, the clinical consequences of these changes are uncertain. There is an increased risk of fractures in children born with spina bifida, but there have not been such reports in other groups.

Reservoir perforation is a lethal complication which is, fortunately, rare. Delayed diagnosis and inadequate treatment may lead to the death of the patient. The diagnosis is best made on clinical grounds. The patient presents with acute abdominal pain and reduced (or absent) urine volume on CIC. Abdominal fluid collections are identified by ultra sound or computerised

tomography. Aspiration of the fluid produces urine and mucus. Unless there is improvement within a few hours on antibiotics and intravenous fluids and antibiotics, laparotomy is essential (*17*).

Cancer is an important long-term risk. A distinction must be made between neoplasms of a retained bladder, an augmenting intestinal segment and an anastomosis between urothelium and intestine.

The anastomotic neoplasm is classically seen in patients with ureterosigmoidostomy (Fig. 17.5). The incidence is 22% at 20 years of follow-up and 33% at 35 years. How many of these are malignant will depend on the vigilance of follow-up, benign lesions probably taking a mean of 5 years to become malignant. In my own series, where most cases are found by surveillance flexible sigmoidoscopy, malignant tumours were found in 7% at 20 years and 9% at 35 years (*10*).

It now is becoming apparent that in reservoirs with faeces excluded, there is still a risk of neoplasia. In a recent review, 49 cases of reservoir malignancies were identified in the literature (Table 17.1) (*18*).

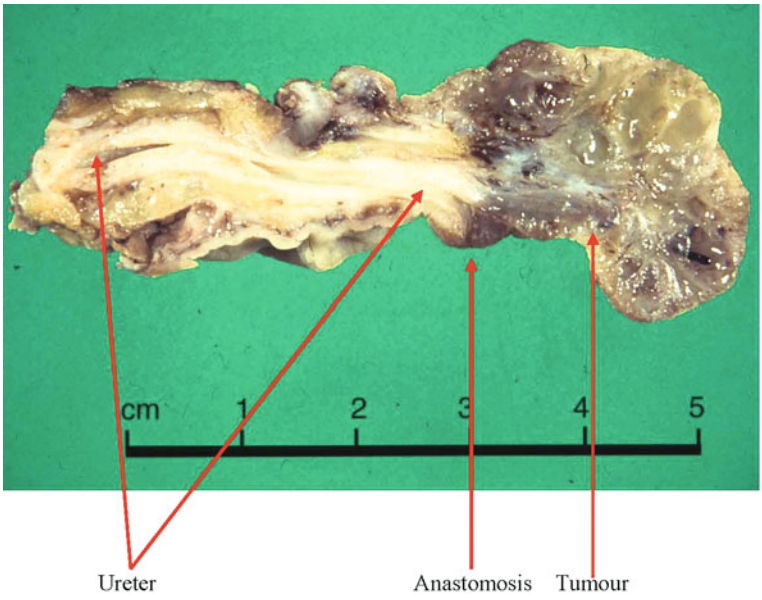

Fig. 17.5. Photograph of a surgical specimen of ureter with an anastomotic tumour removed from a patient with a ureterosigmoidostomy.

More worrying are figures from a long-term follow-up of 260 children who had a bladder augmentation. At a minimum of 10 years, 3 had developed transitional cell carcinoma of the bladder. This incidence of 1.6% is far higher than would be expected in such young individuals (*19*).

Patients with an augmented bladder with urethral access should have a flexible cystoscopy annually from the 12th year. Where access to any reservoir is only through a Mitrofanoff, the problem is more difficult. A standard

Table 17.1
Number of malignancies in various urinary diversions and reconstructions reported in the literature

	Total	*Anastomotic*
Ileocystoplasty	29	18
Colocystoplasty	8	10
Ileal reservoir	1	0
Colonic reservoir	11	5
Ileal conduit	12	

Adapted from Austen and Kalble (*18*)

flexible cystoscope may be too large to pass. A smaller one may have too small a field of view definitely to *exclude* a tumour.

Manipulation of the instrument in the Mitrofanoff channel may damage continence. It may be that diagnosis will have to rely on regular ultra sound, augmented if necessary with a rigid cystoscopy through a suprapubic puncture. The emerging technique of virtual (imaging) endoscopy may prove to be useful.

The intestinal reservoir box

- Serum chloride, bicarbonate and vitamin B12 must be monitored at least annually
- Stones occur in up to 15% of patients
- Perforation is a potentially lethal complication. An acute abdomen in a patient with an intestinal reservoir must be managed aggressively with early surgery
- The risk of malignancy is uncertain (except in those with a ureterosigmoidostomy in whom it is 20% at 20 years), but patients should be monitored if practical

SEXUALITY AND FERTILITY

Disclosure

Pediatric urologists must not try to avoid discussing these aspects with patients and their families. In particular they must not imply that ‘all the problems will be sorted out by the adult urologist’. If a boy has a small or abnormal penis it will come as appalling disappointment to discover that surgery in adolescence will not make it bigger. It is often difficult to predict fertility, but those who are definitely infertile (e.g. absent uterus, ovaries or testes) should be so informed at an appropriate time.

The help of gynecologists, endocrinologist and psychotherapists will often be needed. However, they will be of little use unless they are familiar with the complexities of the diagnoses. This is particularly true of psychotherapists whose normal training will not have covered these conditions. They will need guidance in those conditions where an obvious physical anomaly, such as a short penis, is the cause of severe emotional distress but cannot be corrected.

Hypospadias

There are so many operations for the repair of hypospadias that the nonspecialist may despair of ever understanding even the basic techniques. By adult life, however, most patients have had a satisfactory repair, at least by the standards of the surgeon. Surgeons reviewing their own results give glowing reports such as a straight erection and normal urine stream in 100%. With objective review, the results may be poor in up to 50% (*20*).

The patients are often less satisfied. It would appear that they are least satisfied with the aspects that are least easy to correct, such as penile and glans size and the absence of a normal prepuce (*20*).

There is no consensus on the effect of hypospadias on sexual development, if only because today's adults were reconstructed using techniques that have been superseded.

If there are gross persistent anomalies, especially chordee, intercourse may be impossible (Fig. 17.6). With lesser anomalies, particularly of a cosmetic variety, sexual debut and intercourse may be nearly normal. When compared to boys operated for hernia or for phimosis, there are no differences in the development of standard sexual milestones (*21*). Seminal anomalies may be seen in up to 50%, but there does not seem to be an increased incidence of infertility.

With penoscrotal or perineal hypospadias (often presenting as a disorder of sexual differentiation) intercourse is possible but ejaculation is poor and infertility common.

Exstrophy Males

The penis in exstrophy is short but of normal calibre. An intrinsic part of the anomaly is tight dorsal chordee (Fig. 17.7). If not corrected in infancy, the deformity will prevent penetrative sexual intercourse. In adults, the deformity is investigated by artificial erection, infusing both corpora with saline. Minor defects may be corrected by a ventral Nesbit's procedure, severe ones by a Cantwell-Ransley operation.

Exstrophy Females

The vagina is short and lies in a more horizontal plane than normal. The labia are on the anterior abdominal wall. The introitus is narrow and the clitoris is bifid. Although the position of the labia cannot be changed, the whole

Fig. 17.6. Operative photograph of a man with uncorrected hypospadias and chordee.

Fig. 17.7. Clinical photograph of the penis in a man born with exstrophy to illustrate tight dorsal chordee.

abnormality can be disguised and made completely functional. Patients are normally fertile (*22*).

Uterine prolapse is very common and is unrelated to pregnancy. Procedentia occurs in up to 50% of females, usually, but not always, following pregnancy (*22*).

Posterior Urethral Valves

Like the bladder, the prostate is damaged by back pressure before the valve is resected. This may lead to abnormal semen and poor ejaculation in up to 50% of boys. The seminal abnormality is characterised by lack of liquefaction, low sperm count, poor motility and high pH (up to 9.5). The effect on fertility is unknown but up to a third of patients appear to have some difficulty in achieving paternity. The dilated posterior urethra means that inadequate pressure is established at the beginning of orgasm resulting in less forceful (or absent) ejaculation (*23*).

Fertility

Many anomalies also affect fertility and pregnancy. Advances in reproductive technology have improved matters very considerably, but also bring problems of stress and expense.

Poor male fertility is seen in exstrophy, prune belly syndrome, renal failure, disorders of sexual differentiation and spina bifida. Boys born with a unilateral undescended testis (UDT) probably have normal fertility. Those with bilateral UDT successfully operated in childhood have about a 50% chance of fathering a child.

Poor female fertility is seen in chronic renal failure, disorders of sexual differentiation (including congenital adrenal hyperplasia) and anomalies of uterine development. There is a specific problem in confirming pregnancy in women whose urine is stored in an intestinal reservoir: the standard HCG antibody (blue line) urine test is commonly positive in the absence of pregnancy (*24*). Pregnancy must be confirmed by measurement of the serum HCG.

Pregnancy itself has particular problems in women with spina bifida, enterocystoplasty, re-implanted ureters and exstrophy. However, almost all resolve after delivery. Women should always be advised of such problems but few are deterred from having a baby as a result.

In couples where either partner was born with spina bifida, there is a 1:23 risk of their offspring having a neural tube defect. The risk can be considerably reduced (but not abolished) by giving the mother folic acid 4 mg daily for at least 3 months before conception and for the first trimester.

In women with a GFR below 50 ml/min/1.73 m^2 and a diastolic blood pressure (untreated) above 90 mmHg, there are very significant risks of irreversible deterioration. Between a third and two-thirds will be precipitated into end stage renal failure, about 20% will have worse hypertension and 20% worse proteinuria after delivery.

The sex and fertility box

- The greatest sensitivity is required in discussion of these aspects of adolescence
- Physicians must create an environment in which sexuality and fertility can be explored
- Consultation with a psychologist or sexual counsellor may be needed
- Where possible, physical abnormalities must be corrected by surgery when the patient wishes
- The risks of pregnancy in special situations such as advanced renal failure and spina bifida must be described
- Advice on contraception and the prophylaxis for neural tube defects must be provided

REFERENCES

1. Neild GH, Thomson G, Nitsch D, Woolfson RG, Connolly JO, Woodhouse CRJ. Renal outcome in adults with renal insufficiency and irregular asymmetric kidneys. BMC Nephrology 2004; 5:12–22.
2. Wallace DMA, Rothwell DL, Williams DI. The long term follow up of surgically treated vesicoureteric reflux. British Journal of Urology 1978; 50:479–484.
3. Kohler J, Tencer J, Thysell H, Forsberg L, Hellstrom M. Long term effects of reflux nephropathy on blood pressure and renal function in adults. Nephron Clinical Practice 2003; 93:35–46.
4. Wallace DMA, Rothwell DL, Williams DI. The long term follow up of surgically treated vesicoureteric reflux. British Journal of Urology 1978; 50:479–484.
5. Smellie JM, Prescod NP, Shaw PJ, Risdon RA, Bryant TN. Childhood reflux and urinary infection: a follow-up of 10–41 years in 226 adults. Pediatric Nephrology 1998; 12: 727–736.
6. Parkhouse HF, Woodhouse CRJ. Long term status of patients with posterior urethral valves. Urological Clinics of North America 1990; 17:373–378.
7. Holmdahl G, Sillen U. Boys with posterior urethral valves: outcome concerning renal function, bladder function and paternity at ages 31 to 44. Journal of Urology 2005; 174:1031–1034.
8. Kajbafzadeh AM, Quinn FMJ, Duffy PG, Ransley PG. Augmentation cystoplasty in boys with posterior urethral valves. Journal of Urology 1995; 154:874–877.
9. Woodhouse CRJ, Redgrave NG. Late failure of the reconstructed exstrophy bladder. British Journal of Urology 1996; 77:590–592.
10. Smeulders N, Woodhouse CRJ. Neoplasia in adult exstrophy patients. British Journal of Urology International 2001; 87:623–628.
11. Wagstaff KE, Woodhouse CRJ, Rose GA, Duffy PG, Ransley PG. Blood and urine analysis in patients with intestinal bladders. British Journal of Urology 1991; 68:311–316.
12. Kalloo NB, Jeffs RD, Gearhart JP. Long term nutritional consequences of bowel segment use for lower urinary tract reconstruction in pediatric patients. Urology 1997; 50: 967–971.
13. Robertson WG, Woodhouse CRJ. Metabolic factors in the causation of urinary tract stones in patients with enterocystoplasty. Urological Research 2006; 34(4):231–238.

14. Mingin G, Maroni P, Gerharz EW, Woodhouse CRJ, Baskin LS. Linear growth after enterocystoplasty in children and adolescents: a review. World Journal of Urology 2004; 22:196–199.
15. McDougal WS, Koch MO, Shands C, Price RR. Bony demineralisation following urinary intestinal diversion. Journal of Urology 1988; 140:853–855.
16. Gerharz EW, McDougal WS. Metabolic and functional consequences of urinary diversion through intestinal segments. World Journal of Urology 22[3], 155–234. 2004.
17. Fontaine E, Leaver R, Woodhouse CRJ. Diagnosis of perforated enterocystoplasty. Journal of the Royal Society of Medicine 2003; 96(8):389–392.
18. Austen M, Kalble T. Secondary malignancies in different forms of urinary diversion using isolated gut. Journal of Urology 2004; 172:831–838.
19. Soergel TM, Cain MP, Misseri R, Gardner TA, Koch MO, Rink RC. Transitional cell carcinoma of the bladder following augmentation cystoplasty for the neuropathic bladder. Journal of Urology 2004; 172:1649–1652.
20. Mureau MAM, Slijper FME, Koos Slob A, Verhulst FC, Nijman RJM. Satisfaction with penile appearance after hypospadias surgery: the patient and surgeon view. Journal of Urology 1996; 155:703–706.
21. Aho MO, Tammela OKT, Somppi EMJ, Tammela TLJ. A long term comparative follow up study of voiding, sexuality and satisfaction among men operated for hypospadias and phimosis during childhood. European Journal of Urology 2000; 37:95–101.
22. Woodhouse CRJ. The gynaecology of exstrophy. British Journal of Urology International 1999; 83(Suppl. 3):34–38.
23. Woodhouse CRJ, Reilly JM, Bahadur G. Sexual function and fertility in patients treated for posterior urethral valves. Journal of Urology 1989; 142:586–588.
24. Nethercliffe J, Trewick A, Samuell C, Leaver R, Woodhouse CRJ. False positive pregnancy tests in patients with enterocystoplasties. British Journal of Urology International 2001; 87:780–782.
25. Blumenthal S, Epps RP, Heavenrich R. report of the task force on blood pressure control in children: standards for blood pressure. Paediatrics 1977; 58(Supplement):802–803.

18 Laparoscopy in the Pediatric Population

Glenn Cannon and Carlos R. Estrada

Abstract Although once limited to the adult population, laparoscopic applications to urologic surgery are now being successfully applied to children of all ages. The current role of laparoscopy in children requiring pyeloplasty, orchidopexy, renal ablative procedures, ureteral reimplantation, lower urinary tract reconstruction, and varicocelectomy are reviewed. Newer applications of robotic assistance are also discussed with emphasis on published results. Future research will continue to define the safest and most efficacious applications of laparoscopy in pediatric urology.

Keywords Laparoscopy · Pediatrics · Urology · Ureteral obstruction · Urinary bladder · Neurogenic · Vesico-uretral reflux · Hydronephrosis · Testis · undescended · Varicocele · Robotics

INTRODUCTION

Laparoscopic procedures have blossomed in the field of pediatric urology over the last 15 years. As visualization and instrumentation have improved, laparoscopic techniques have now been successfully applied to pyeloplasty, renal ablative procedures, orchidopexy, lower urinary tract reconstruction, ureteral reimplantation, and varicocelectomy. Children are now able to benefit from the laparoscopic benefits of improved cosmesis and decreased postoperative pain that have long been known in adult surgery. Robotic-assistance is now being applied to almost every laparoscopic procedure in pediatric urology and further experience will determine the ideal role it will play in the future.

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ANESTHETIC CONCERNS

When performing laparoscopy in children, unique physiologic factors must be taken into account. This is especially true in retroperitoneal procedures because the retroperitoneum offers less of a barrier to CO_2 accumulation and absorption than the peritoneal space (*1*). Factors such as heart rate dependent cardiac output, altered total thoracic compliance, and susceptibility to postoperative respiratory muscle fatigue all decrease the margin of safety of anesthesia in infants and children (*2*, *3*). Halachmi et al. performed a retrospective review of the hemodynamic and respiratory effect of pediatric urological laparoscopic surgery (*4*). In their series of 62 patients, they noted that upon CO_2 insufflation, there was a significant reduction in O_2 saturation, increase in end tidal CO_2, and increase in peak airway pressure. The same group later performed a prospective study of 18 healthy children undergoing elective laparoscopic retroperitoneal urological surgery with a standard anesthetic regime (*5*). Upon insufflation of CO_2, there were statistically significant increases in peak airway pressure, end tidal CO_2, and mean arterial pressure. Each trended toward baseline at the conclusion of the procedure.

In higher risk children with pulmonary pathology, increased attention must be given to arterial pCO_2 levels during CO_2 insufflation (*2*). El-Ghoneimi et al. reported a series of 12 retroperitoneal nephrectomies in nine high-risk children with end stage renal disease (*6*). Although upon CO_2 insufflation systolic arterial pressure and end tidal CO_2 were significantly increased, there were no complications and mean hospital stay was 5.2 days. Another group who have been considered at higher risk for laparoscopy are children with ventriculoperitoneal shunts. Jackman et al. reviewed 19 laparoscopic operations in children with ventriculoperitoneal shunts and found no evidence of clinically significant increased intracranial pressure (*7*).

LAPAROSCOPIC PYELOPLASTY

The most common cause of neonatal hydronephrosis is ureteropelvic junction (UPJ) obstruction (*8*). Since Anderson and Haynes first described open pyeloplasty in 1949 (*9*), the procedure has long been the standard in repair of UPJ obstruction with reported success rates of 85–98% (*10*–*14*). Since its initial description by Peters in 1995 (*15*), laparoscopic pyeloplasty has become a standard treatment of ureteropelvic junction obstruction in children. The operation can be performed with either a transperitoneal or retroperitoneal approach. The transperitoneal approach offers the benefit of a larger working space. The retroperitoneal offers a potential benefit of not entering the peritoneum and risking abdominal organ injury (*16*). Canon et al. performed a retrospective review comparing the transperitoneal and retroperitoneal approached to laparoscopic pyeloplasty in children (*17*). They found no difference in success and complication rates between the two

approaches. Shoma et al. performed a prospective, randomized trial comparing the two approaches and demonstrated good functional outcome and low morbidity regardless of the approach (*18*). Therefore, the decision to perform either transperitoneal or retroperitoneal laparoscopic pyeloplasty is currently best determined by an individual surgeon's personal experience and comfort level.

Since the initial case series reported by Tan in 1999 (*19*), multiple series have demonstrated that laparoscopic pyeloplasty in children has similar success rates compared to open pyeloplasty (*16*, *20*–*26*). Although with some surgeons the procedure was initially limited to older children (*16*, *19*), the development of finer instrumentation has allowed the procedure to be applied successfully in younger children and infants. Cascio et al. reported an 86% success rate in laparoscopic dismembered pyeloplasty in children under 2 years of age (*27*). Kutikov et al. reported a 100% success rate of laparoscopic pyeloplasty in eight children under 6 months of age (*28*).

Although the number of surgeons performing laparoscopic pyeloplasty has increased in recent years, limited diffusion of the technique has restricted its availability (*29*). One of the greatest challenges to performing laparoscopic pyeloplasty is the difficulty in performing intracorporeal suturing with standard laparoscopic instruments. Mastery of this skill is associated with a steep learning curve that can be significantly shortened by performing laparoscopic pyeloplasty with robotic assistance (Fig. 18.1) (*30*–*32*).

The introduction and widespread availability of the da Vinci Surgical System (Intuitive, Sunnyvale, CA) have led to an increase in robotic laparoscopic procedures in pediatric urology. Compare to conventional laparoscopy, the da Vinci System offers 90 degrees of articulation, 7 degrees of freedom, motion scaling, and tremor reduction (*33*). In addition to the standard 8-mm instruments, 5-mm ones have been developed targeting pediatric urology and pediatric general surgical applications (Fig. 18.2). Robotic laparoscopic applications in pediatric urology include pyeloplasty, orchidopexy, varicocelectomy, total and partial nephrectomy, ureteral reimplantation, and bladder reconstructive surgery (*34*).

Currently, the robotic procedure with the most published information is robotic-assisted laparoscopic pyeloplasty. Yee et al. compared eight pediatric patients who underwent robotic pyeloplasty with eight age-matched patients who underwent open pyeloplasty (*35*). They demonstrated decreased length of hospitalization and decreased opioid requirement with the robotic procedure, but longer operative time. Lee et al. compared a larger cohort of 33 children who underwent robotic laparoscopic pyeloplasty with age-matched children who underwent open pyeloplasty (*36*). They also demonstrated decreased length of stay and opioid requirements with the robotic-assisted procedure and similar operative times compared to open pyeloplasty. It has been stated that robotic assisted pyeloplasty is associated with a longer operative time than conventional laparoscopic pyeloplasty (*37*). However, in multiple studies in both adults and children,

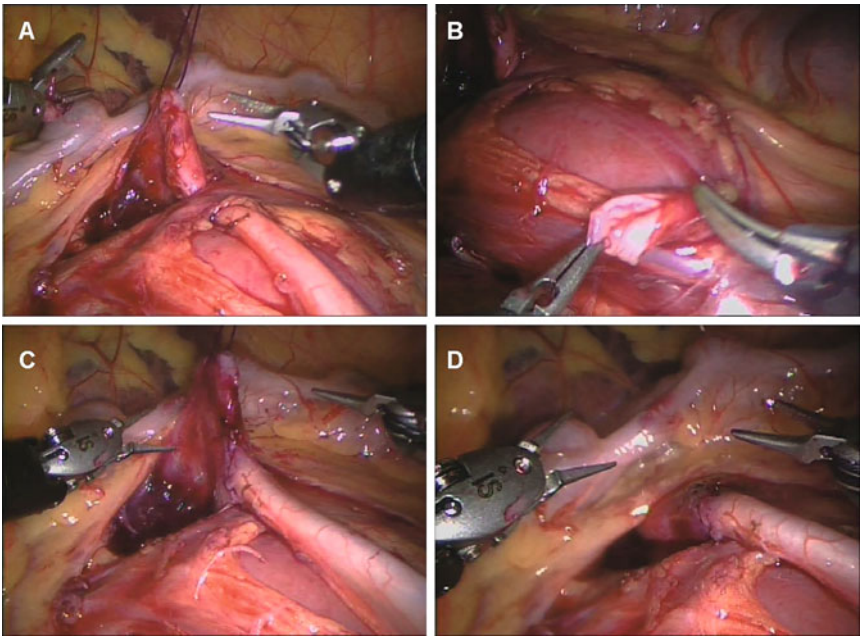

Fig. 18.1. Robotic assisted laparoscopic dismembered pyeloplasty. This case demonstrates lower pole crossing vessels causing a UPJ obstruction. (**a**) The UPJ is exposed through a transmesenteric approach and is retracted using a "hitch stitch." The crossing vessels are clearly seen. (**b**) Following transection of the ureter, it is spatulated on its lateral aspect. (**c**) The ureteropelvic anastomosis is completed with the "hitch stitch" in place. In this case 6–0 polyglecaprone (Monocryl) running sutures were utilized. (**d**) The appearance of the reconstructed UPJ transposed in front of the lower pole crossing vessels.

robotic-assisted pyeloplasty has been demonstrated to have shorter operative times than standard laparoscopic pyeloplasty but have comparable complications and results (*31*, *38*, *39*).

As availability of and experience with the da Vinci Surgical System increase, indications for robotic assisted pyeloplasty are expanding to difficult situations where conventional laparoscopic pyeloplasty would be exceedingly difficult or impossible. Successful pediatric robotic assisted pyeloplasty procedures have been reported in reoperative procedures (*40*) and post-traumatic UPJ disruption (*41*). As availability of the da Vinci Surgical System increases, robotic-assisted procedures will become more common when performing laparoscopic pyeloplasty.

LAPAROSCOPIC ORCHIOPEXY

The surgical management of undescended testis has changed significantly in the last 15 years. In 1995, Docimo reviewed 64 articles pertaining to

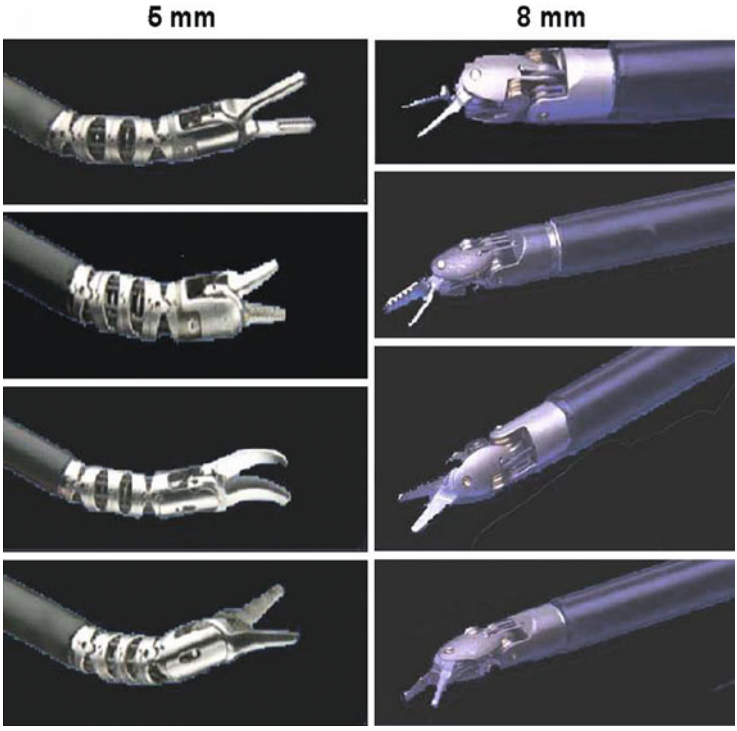

Fig. 18.2. 5-mm and 8-mm da Vinci instruments. There is no difference in the maneuverability between the two sizes. The 5-mm instruments do provide an advantage when working in small spaces, which are frequently encountered in pediatric urology.

8,425 undescended testes to examine success rates reported for orchiopexy (*42*). Success rates by procedure were 89% for inguinal, 67% for Fowler-Stephens, 77% for staged Fowler-Stephens, 81% for transabdominal, 73% for 2-stage, and 84% for microvascular orchidopexy. The success rate for testes with an abdominal position was only 74% leading to the conclusion that efforts could be made to improve orchidopexy in proximal undescended testes.

Beginning in the 1990s, interest began in performing laparoscopic orchidopexy. Initial reports had greater than 90% success rates, but low patient numbers (*43–49*). Baker et al. combined and analyzed the results of laparoscopic orchidopexy from centers with a large experience with smaller series to determine the expected success rate (*50*). In their multi-institutional review, primary laparoscopic orchidopexy had a success rate of 97.8% with a mean follow-up of 7.7 months.

Recent literature has focused on factors that predict success in laparoscopic orchidopexy. Banieghbal and Davies reported that if the testis can be mobilized to where it can be stretched over the contralateral inguinal ring, successful orchidopexy can be carried out 100% of the time (*51*). However,

this finding has been questioned. Yucel et al. reported a series of 46 testes treated with laparoscopic orchidopexy and stated that location within 2 cm of the inguinal ring and mobility to the contralateral ring did not predict ability to bring the testis into the low scrotum (*52*). El-Anany et al. have noted that older children have less stretch to their spermatic vessels and may be more likely to require division of the spermatic vessels (*53*).

Diagnostic laparoscopy for undescended testes and laparoscopic orchidopexy are now some of the most common laparoscopic procedures performed in pediatric urology. Cost analysis has demonstrated that initial laparoscopic evaluation of the clinically nonpalpable testis is cost saving compared to initial inguinal-scrotal exploration (*54*). Further research is needed to best determine the factors that predict success either with or without spermatic vessel ligation.

LAPAROSCOPIC RENAL ABLATIVE SURGERY

Since the initial description of a laparoscopic heminephrectomy in a 14-year-old by Jordan and Winslow in 1993 (*55*), a large amount of literature has been devoted to laparoscopic renal ablative surgery in children. Janetschek et al. presented the first series of pediatric laparoscopic heminephrectomy (*56*). In 12 cases, 7 upper renal poles were removed for ectopic refluxing megaureter and obstructive ureteroceles. Five lower poles were removed for reflux nephropathy. Although their blood loss was minimal (10–30 ml) and there were no complications and mean operative time was 222 min. The authors concluded that this technically demanding procedure should only be performed at specialized centers. Horowitz et al. later reported a series of 14 laparoscopic upper pole heminephrectomies with a mean operative time of 100 min (*57*).

To assess for potential benefits of laparoscopic renal ablative surgery over open procedures, Robinson et al. retrospectively compared 22 consecutive partial nephrectomies of which 11 were performed laparoscopically and 11 performed open in a nonrandomized fashion. Although the mean operative time was significantly longer for the laparoscopic group (200 min vs. 114 min), there was no difference in mean hospital stay. Patients in the laparoscopic group had a significantly less opioid requirement than the open group. Piaggio et al. compared intraperitoneal laparoscopic partial nephrectomy to an open retroperitoneal approach (*58*). They noted that length of hospitalization was shorter in the laparoscopic group and stated that the procedure is feasible even in small infants.

Success in laparoscopic partial nephrectomy has also been reported via a retroperitoneal approach (*59*, *60*). Lee et al. performed an age-matched comparison of pediatric patients undergoing retroperitoneal laparoscopic partial nephrectomy to open surgery (*61*). Compared to open partial nephrectomy, the laparoscopic approach was associated with equivalent operative times and significantly less length of stay and postoperative opioid requirements.

Although ultimately the surgical approach will be chosen by an individual surgeon's comfort level and experience, Borzi and Yeung proposed selecting an approach based on the specific type of procedure performed (*62*). Reporting an experience of 179 laparoscopic procedures, they recommended a posterior retroperitoneal approach for isolated renal excision without extended ureterectomy, a lateral retroperitoneal approach for complete ureterectomy or access to horseshoe and pelvic kidneys, and a transperitoneal approach when complete moiety excision with lower urinary reconstruction is planned. Castellan et al. also reported their experience utilizing both transperitoneal and retroperitoneal heminephrectomy (*63*). They noted that although there was no difference in complication rate between the two approaches, 80% of their complications occurred in children younger than 1 year. The posterior prone retroperitoneal approach has been recommended for children with end stage renal disease who may require immediate peritoneal dialysis (*64*, *65*). Martinez Urrutia et al. have reported bilateral laparoscopic nephrectomy with simultaneous peritoneal dialysis catheter implantation (*66*).

As experience with laparoscopic nephrectomy and heminephroureterectomy increases, operative time and estimated blood loss can improve. Yucel et al. retrospectively reviewed their experience with laparoscopic ablative renal surgery performed by one surgeon over a 6-year period (*67*). At the 4th year of their experience, they noted a statistically significant improvement in operative time for laparoscopic nephrectomy and in estimated blood loss for laparoscopic heminephroureterectomy. They concluded that their experience should continue to encourage pediatric urologists to perform laparoscopic renal ablative surgery. Increased experience with pediatric laparoscopic renal surgery has also led to expanded indications for its performance such as laparoscopic nephrectomy for giant hydronephrosis of the kidney (*68*, *69*).

With its decreased length of stay, decreased postoperative opioid requirements, improved cosmesis, and equivalent operative times to open surgery, laparoscopic nephrectomy, and heminephrectomy have become widespread procedures in pediatric urology. In a cost analysis from the United Kingdom, the laparoscopic approach to nephrectomy in children was 54% less expensive than the open approach (*70*). Currently, the da Vinci Surgical System is starting to be utilized with laparoscopic heminephrectomy and future research will determine its utility compared to conventional laparoscopy.

LAPAROSCOPIC LOWER URINARY TRACT RECONSTRUCTION

Laparoscopic lower urinary tract reconstruction has been slow in gaining widespread acceptance due to the perceived difficulty and intricate nature of such procedures. In 1993, Jordan and Winslow first reported a

laparoscopic-assisted appendicovesicostomy in a 15-year-old girl (*71*). The appendix and cecum were mobilized laparoscopically but an open cystotomy was performed for the anastomosis. Two years later Docimo et al. reported performing a laparoscopic bladder augmentation with stomach utilizing a stapled technique (*72*). In 1999, Hedican et al. reported a series of eight pediatric patients undergoing laparoscopic assisted lower urinary tract reconstruction including bladder augmentation, appendicovesicostomy, and Malone antegrade continence enema procedures (*73*). Laparoscopy was utilized for mobilization and appendiceal harvesting while the reconstruction was completed through a Pfannensteil or low-midline incision. Their operative time was comparable to similar open procedures and they experienced minimal blood loss. Cadeddu and Docimo later compared laparoscopic-assisted to open continent stoma procedures (*74*). Compared to the laparoscopic group, the patients who underwent the open procedure had similar operative times but took longer to resume a regular diet (5.6 days vs. 2.3 days) and had a longer length of stay (7.4 days vs. 4.1 days).

Beginning with the initial reports by Meng et al. and Elliott et al. of performing a complete intracorporeal enterocystoplasty (*75*, *76*), urologists have begun to focus on performing lower urinary tract reconstruction entirely in a laparoscopic fashion. Casale et al. followed by Hsu and Shortliffe each reported performing a complete intracorporeal laparoscopic appendicovesicostomy (*77*, *78*). Subsequently, multiple series have reported safety and success with complete intracorporeal laparoscopic augmentation ileocystoplasty either with or without a Malone antegrade continence enema procedure at the same time (*79*, *80*). Utilizing fewer ports and transabdominal fixating sutures have allowed the procedure to overcome the limited working space within children (*81*).

The application of the robotic da Vinci Surgical System to laparoscopic lower urinary tract reconstruction represents a new development for these challenging laparoscopic procedures. Pedraza et al. reported performing a robotic laparoscopic appendicovesicostomy in a 7-year-old boy with a history of posterior urethral valves (*82*). It is current practice at our institution to perform laparoscopic lower urinary tract reconstruction with robotic assistance. Further experience is needed to determine the equivalency or superiority of robotic-assisted over conventional laparoscopic enterocystoplasty or appendicovesicostomy.

LAPAROSCOPIC URETERAL REIMPLANTATION

The first report of laparoscopic correction of vesicoureteral reflux in a porcine model was by Atala et al. in 1993 (*83*). By applying a modification of the Lich extravesical approach, their success rate was 100% at 5 months of follow-up. McDougall et al. later reported another porcine series utilizing laparoscopic extravesical repair (*84*). Six months postoperatively, five out of six pigs had no reflux and one pig had residual grade I reflux. Baldwin

et al. later reported another porcine series in which laparoscopic extravesical ureteral reimplantation was simplified by transposing the ureters inside the bladder with no attempt to cover them with urothelium (*85*). Their success rate at complete resolution of reflux was 100% six months postoperatively.

Ehrlich et al. reported the first case series of two children who underwent laparoscopic extravesical ureteral reimplantation (*86*). Although there were no complications, no follow up information was provided. Janetschek et al. later reported a series of six girls who underwent laparoscopic Lich-Gregoir reimplantation with one girl approached in an extraperitoneal fashion (*87*). Two of the six children experienced ureteral stenosis and the authors concluded that the laparoscopic procedure offered no benefit over the conventional open procedure.

Newer research has focused on performing laparoscopic intravesical ureteral reimplantation. Yeung et al. reported a novel series of 16 children with vesicoureteral reflux who underwent transabdominal, intravesical cross-trigonal ureteral reimplantation utilizing CO_2 insufflation within the bladder (*88*). They achieved a 96% success rate at complete resolution of reflux with a mean operating time of 136 min. Kutikov et al. reported a larger series of 32 patients who underwent laparoscopic transvesical reimplantation utilizing a pure laparoscopic approach (*89*). Their success rate was 92.6% for vesicoureteral reflux and 80% for primary obstructing megaureter. However, postoperative urinary leak occurred in 12.5% and ureteral stricture occurred in 6.3%. They noted that all but one of the complications occurred in patients 2 years or younger.

Given the complexity and difficulty of performing laparoscopy within such a small space, several groups have examined utilizing robotic assistance to perform laparoscopic intravesical ureteral reimplantation. Peters and Woo initially reported the use of robotic-assistance with laparoscopic intravesical ureteral reimplantation with successful results and no port site leakage (*90*). Our institution is currently building a series of robotic-assisted intravesical ureteral reimplantations. As experience increases, more will be known about the outcomes of this newer procedure that offers superior cosmesis to traditional open ureteral reimplantation.

LAPAROSCOPIC VARICOCELECTOMY

Varicoceles are found in approximately 15% of adolescent males with a significant left-sided predominance (*91*). Steeno et al. reported ipsilateral volume loss in 34.4% of boys with a grade 2 varicocele and 81.2% of boys with a grade 3 varicocele.

Prior to the 1990s, the traditional treatment for varicoceles in children was high retroperitoneal ligation of the spermatic vein. Although associated with a low recurrence rate, due to the lack of lymphatic sparing this procedure was associated with a high postoperative hydrocele rate (*92*). The initial report of laparoscopic varicocele ligation was by Sanchez et al. in

1988 who concluded that it was more expensive and of no additional benefit to open varicoceletomy. In 1992, Hagood et al. reported the first series of patients undergoing laparoscopic varicocelectomy (*93*). In 10 procedures, they reported a 100% success rate.

Multiple subsequent series have demonstrated the efficacy and advantages of laparoscopic varicoceletomy in children and adolescents (*94*–*100*). However, others have reported decreased efficacy, increase cost, longer operative times, and higher complications compared to open varicocele ligation (*101*–*103*). Riccabona et al. performed a retrospective review of 128 varicocelectomies performed with 4 different techniques: laparoscopic, inguinal, Palomo, and modified Palomo (suprainginual ligation of artery and vein with microsurgical sparing of lymphatics) (*104*). In their laparoscopic group, preservation of the testicular artery was only possible 57% of the time. Their laparoscopic group had a recurrence rate of 11%, significantly less than 2% with their modified Palomo technique. They sated that laparoscopic varicocelectomy had been abandoned at their center in favor of the modified Palomo technique.

To resolve the debate surrounding laparoscopic varicoceletomy, Podkamenev et al. performed a prospective, randomized controlled trial of 654 boys with either grade II or III left-sided varicoceles comparing laparoscopic varicocelectomy with dye-assisted lymphatic-sparing high retroperitoneal spermatic vein ligation (*105*). Although there was no difference in recurrence between the two techniques, the laparoscopic approach was associated with significantly less hydrocele formation, wound complications, operative time, and postoperative pain. McManus et al. retrospectively compared laparoscopic varicocelectomy with subinguinal microscopic varicocelectomy, a procedure associated with less recurrence and hydrocele formation than the Palomo procedure (*106*). In their series laparoscopic varicocelectomy had shorter operative times and fewer negative outcomes compared to subinguinal microscopic varicoceletomy. This translated into lower direct patient costs for the laparoscopic technique. VanderBrink et al. more recently performed a retrospective review of lymphatic sparing laparoscopic varicocelectomy vs. subinguinal microscopic varicocelectomy (*107*). With a mean follow-up time of 2 years, there was no difference in recurrence or hydrocele formation between the two techniques. However, the mean operative time for the laparoscopic group (51 min) was significantly shorter than the subinguinal group (140 min).

In an effort to make laparoscopic varicocelectomy even less invasive, several authors have reported on completing the procedure using less than three trochars. Multiple authors have demonstrated success equivalent to open surgery using only two trochars (*108*, *109*). With a mean follow-up of 8 weeks, Kaouk and Palmer reported 100% success in three adolescents undergoing laparoscopic varicocelectomy through a multichannel single laparoscopic port inserted at the umbilicus (*110*). Messina et al. have reported good results with a mean follow-up of 23.4 months in 40 children

and adolescents undergoing single-trochar varicocelectomy (*111*). Further study of the single-trochar technique is needed before it achieves widespread application in laparoscopic varicocelectomy.

CONCLUSION

Minimally invasive approaches have been demonstrated to be successful in a variety of surgical procedures in pediatric urology. In the past, availability of these procedures was limited to select academic centers. Currently, the majority of pediatric urology fellowships now offer extensive laparoscopic training (*67*). As this new generation of pediatric urologists establish their practices, laparoscopic alternatives to open surgery will become more available and further research will continue to determine its best applications.

REFERENCES

1. Streich B, Decailliot F, Perney C, Duvaldestin P. Increased carbon dioxide absorption during retroperitoneal laparoscopy. Br J Anaesth 2003;91(6):793–6.
2. Wedgewood J, Doyle E. Anaesthesia and laparoscopic surgery in children. Paediatr Anaesth 2001;11(4):391–9.
3. McAuliffe G, Bissonnette B, Cavalle-Garrido T, Boutin C. Heart rate and cardiac output after atropine in anaesthetised infants and children. Canadian journal of anaesthesia. J Can d'anesthesie 1997;44(2):154–9.
4. Halachmi S, El-Ghoneimi A, Bissonnette B, et al. Hemodynamic and respiratory effect of pediatric urological laparoscopic surgery: a retrospective study. J Urol 2003;170 (4 Pt 2):1651–4; discussion 4.
5. Lorenzo AJ, Karsli C, Halachmi S, et al. Hemodynamic and respiratory effects of pediatric urological retroperitoneal laparoscopic surgery: a prospective study. J Urol 2006;175(4):1461–5.
6. El-Ghoneimi A, Sauty L, Maintenant J, Macher MA, Lottmann H, Aigrain Y. Laparoscopic retroperitoneal nephrectomy in high risk children. J Urol 2000;164(3 Pt 2): 1076–9.
7. Jackman SV, Weingart JD, Kinsman SL, Docimo SG. Laparoscopic surgery in patients with ventriculoperitoneal shunts: safety and monitoring. J Urol 2000;164(4):1352–4.
8. Brown T, Mandell J, Lebowitz RL. Neonatal hydronephrosis in the era of sonography. AJR 1987;148(5):959–63.
9. Anderson JC, Hynes W. Retrocaval ureter; a case diagnosed pre-operatively and treated successfully by a plastic operation. Br J Urol 1949;21(3):209–14.
10. MacNeily AE, Maizels M, Kaplan WE, Firlit CF, Conway JJ. Does early pyeloplasty really avert loss of renal function? A retrospective review. J Urol 1993;150(2 Pt 2): 769–73.
11. Shaul DB, Cunningham JA, Lowe P, Skaist LB, Hardy BE. Infant pyeloplasty is a low-risk procedure. J Pediatr Surg 1994;29(2):343–7.
12. Salem YH, Majd M, Rushton HG, Belman AB. Outcome analysis of pediatric pyeloplasty as a function of patient age, presentation and differential renal function. J Urol 1995;154(5):1889–93.
13. Austin PF, Cain MP, Rink RC. Nephrostomy tube drainage with pyeloplasty: is it necessarily a bad choice? J Urol 2000;163(5):1528–30.
14. Houben CH, Wischermann A, Borner G, Slany E. Outcome analysis of pyeloplasty in infants. Pediatr Surg Int 2000;16(3):189–93.

15. Peters CA, Schlussel RN, Retik AB. Pediatric laparoscopic dismembered pyeloplasty. J Urol 1995;153(6):1962–5.
16. Bonnard A, Fouquet V, Carricaburu E, Aigrain Y, El-Ghoneimi A. Retroperitoneal laparoscopic versus open pyeloplasty in children. J Urol 2005;173(5):1710–3; discussion 3.
17. Canon SJ, Jayanthi VR, Lowe GJ. Which is better – retroperitoneoscopic or laparoscopic dismembered pyeloplasty in children? J Urol 2007;178(4 Pt 2):1791–5; discussion 5.
18. Shoma AM, El Nahas AR, Bazeed MA. Laparoscopic pyeloplasty: a prospective randomized comparison between the transperitoneal approach and retroperitoneoscopy. J Urol 2007;178(5):2020–4; discussion 4.
19. Tan HL. Laparoscopic Anderson-Hynes dismembered pyeloplasty in children. J Urol 1999;162(3 Pt 2):1045–7; discussion 8.
20. El-Ghoneimi A, Farhat W, Bolduc S, et al. Laparoscopic dismembered pyeloplasty by a retroperitoneal approach in children. BJU Int 2003;92(1):104–8; discussion 8.
21. Casale P, Grady RW, Joyner BD, Zeltser IS, Figueroa TE, Mitchell ME. Comparison of dismembered and nondismembered laparoscopic pyeloplasty in the pediatric patient. J Endourol 2004;18(9):875–8.
22. Schier F. Laparoscopic Anderson-Hynes pyeloplasty in children. Pediatr Surg Int 1998;13(7):497–500.
23. Yeung CK, Tam YH, Sihoe JD, Lee KH, Liu KW. Retroperitoneoscopic dismembered pyeloplasty for pelvi-ureteric junction obstruction in infants and children. BJU Int 2001;87(6):509–13.
24. Metzelder ML, Schier F, Petersen C, Truss M, Ure BM. Laparoscopic transabdominal pyeloplasty in children is feasible irrespective of age. J Urol 2006;175(2):688–91.
25. Reddy M, Nerli RB, Bashetty R, Ravish IR. Laparoscopic dismembered pyeloplasty in children. J Urol 2005;174(2):700–2.
26. Lam PN, Wong C, Mulholland TL, Campbell JB, Kropp BP. Pediatric laparoscopic pyeloplasty: 4-year experience. J Endourol 2007;21(12):1467–71.
27. Cascio S, Tien A, Chee W, Tan HL. Laparoscopic dismembered pyeloplasty in children younger than 2 years. J Urol 2007;177(1):335–8.
28. Kutikov A, Resnick M, Casale P. Laparoscopic pyeloplasty in the infant younger than 6 months – is it technically possible? J Urol 2006;175(4):1477–9; discussion 9.
29. Peters CA. Editorial comment. J Urol 2005;173:1713.
30. Bentas W, Wolfram M, Brautigam R, et al. Da Vinci robot assisted Anderson-Hynes dismembered pyeloplasty: technique and 1 year follow-up. World J Urol 2003;21(3):133–8.
31. Gettman MT, Peschel R, Neururer R, Bartsch G. A comparison of laparoscopic pyeloplasty performed with the daVinci robotic system versus standard laparoscopic techniques: initial clinical results. Eur Urol 2002;42(5):453–7; discussion 7–8.
32. Gettman MT, Neururer R, Bartsch G, Peschel R. Anderson-Hynes dismembered pyeloplasty performed using the da Vinci robotic system. Urology 2002;60(3):509–13.
33. Endowrist Instruments. (Accessed 4/20/07, at http://www.intuitivesurgical.com/products/endowrist_instruments/index.aspx.)
34. Estrada CR, Passerotti CC. [Robotic surgery in pediatric urology]. Arch Esp Urol 2007;60(4):471–9.
35. Yee DS, Shanberg AM, Duel BP, Rodriguez E, Eichel L, Rajpoot D. Initial comparison of robotic-assisted laparoscopic versus open pyeloplasty in children. Urology 2006;67(3):599–602.
36. Lee RS, Retik AB, Borer JG, Peters CA. Pediatric robot assisted laparoscopic dismembered pyeloplasty: comparison with a cohort of open surgery. J Urol 2006;175(2):683–7; discussion 7.
37. Link RE, Bhayani SB, Kavoussi LR. A prospective comparison of robotic and laparoscopic pyeloplasty. Ann Surg 2006;243(4):486–91.
38. Olsen LH, Jorgensen TM. Computer assisted pyeloplasty in children: the retroperitoneal approach. J Urol 2004;171(6 Pt 2):2629–31.

39. Olsen LH, Rawashdeh YF, Jorgensen TM. Pediatric robot assisted retroperitoneoscopic pyeloplasty: a 5-year experience. J Urol 2007;178(5):2137–41; discussion 41.
40. Passerotti CC, Nguyen HT, Eisner BH, Lee RS, Peters CA. Laparoscopic reoperative pediatric pyeloplasty with robotic assistance. J Endourol 2007;21(10):1137–40.
41. Yee DS, Klein RB, Shanberg AM. Case report: robot-assisted laparoscopic reconstruction of a ureteropelvic junction disruption. J Endourol 2006;20(5):326–9.
42. Docimo SG. The results of surgical therapy for cryptorchidism: a literature review and analysis. J Urol 1995;154(3):1148–52.
43. Lindgren BW, Darby EC, Faiella L, et al. Laparoscopic orchiopexy: procedure of choice for the nonpalpable testis? J Urol 1998;159(6):2132–5.
44. Merguerian PA, Mevorach RA, Shortliffe LD, Cendron M. Laparoscopy for the evaluation and management of the nonpalpable testicle. Urology 1998;51(5A Suppl): 3–6.
45. Lindgren BW, Franco I, Blick S, et al. Laparoscopic Fowler-Stephens orchiopexy for the high abdominal testis. J Urol 1999;162(3 Pt 2):990–3; discussion 4.
46. Docimo SG, Moore RG, Adams J, Kavoussi LR. Laparoscopic orchiopexy for the high palpable undescended testis: preliminary experience. J Urol 1995;154(4): 1513–5.
47. Jordan GH, Winslow BH. Laparoscopic single stage and staged orchiopexy. J Urol 1994;152(4):1249–52.
48. Bloom DA. Two-step orchiopexy with pelviscopic clip ligation of the spermatic vessels. J Urol 1991;145(5):1030–3.
49. Caldamone AA, Amaral JF. Laparoscopic stage 2 Fowler-Stephens orchiopexy. J Urol 1994;152(4):1253–6.
50. Baker LA, Docimo SG, Surer I, et al. A multi-institutional analysis of laparoscopic orchidopexy. BJU Int 2001;87(6):484–9.
51. Banieghbal B, Davies M. Laparoscopic evaluation of testicular mobility as a guide to management of intra-abdominal testes. World J Urol 2003;20(6):343–5.
52. Yucel S, Ziada A, Harrison C, Wilcox D, Baker L, Snodgrass W. Decision making during laparoscopic orchiopexy for intra-abdominal testes near the internal ring. J Urol 2007;178(4 Pt 1):1447–50; discussion 50.
53. El-Anany F, Gad El-Moula M, Abdel Moneim A, et al. Laparoscopy for impalpable testis: classification-based management. Surg Endosc 2007;21(3):449–54.
54. Lorenzo AJ, Samuelson ML, Docimo SG, Baker LA, Lotan Y. Cost analysis of laparoscopic versus open orchiopexy in the management of unilateral nonpalpable testicles. J Urol 2004;172(2):712–6.
55. Jordan GH, Winslow BH. Laparoendoscopic upper pole partial nephrectomy with ureterectomy. J Urol 1993;150(3):940–3.
56. Janetschek G, Seibold J, Radmayr C, Bartsch G. Laparoscopic heminephroureterectomy in pediatric patients. J Urol 1997;158(5):1928–30.
57. Horowitz M, Shah SM, Ferzli G, Syad PI, Glassberg KI. Laparoscopic partial upper pole nephrectomy in infants and children. BJU Int 2001;87(6):514–6.
58. Piaggio L, Franc-Guimond J, Figueroa TE, Barthold JS, Gonzalez R. Comparison of laparoscopic and open partial nephrectomy for duplication anomalies in children. J Urol 2006;175(6):2269–73.
59. Wallis MC, Khoury AE, Lorenzo AJ, Pippi-Salle JL, Bagli DJ, Farhat WA. Outcome analysis of retroperitoneal laparoscopic heminephrectomy in children. J Urol 2006;175(6):2277–82.
60. Valla JS, Breaud J, Carfagna L, Tursini S, Steyaert H. Treatment of ureterocele on duplex ureter: upper pole nephrectomy by retroperitoneoscopy in children based on a series of 24 cases. Eur Urol 2003;43(4):426–9.
61. Lee RS, Retik AB, Borer JG, Diamond DA, Peters CA. Pediatric retroperitoneal laparoscopic partial nephrectomy: comparison with an age matched cohort of open surgery. J Urol 2005;174(2):708–11; discussion 12.
62. Borzi PA, Yeung CK. Selective approach for transperitoneal and extraperitoneal endoscopic nephrectomy in children. J Urol 2004;171(2 Pt 1):814–6; discussion 6.

63. Castellan M, Gosalbez R, Carmack AJ, Prieto JC, Perez-Brayfield M, Labbie A. Transperitoneal and retroperitoneal laparoscopic heminephrectomy – what approach for which patient? J Urol 2006;176(6 Pt 1):2636–9; discussion 9.
64. Gundeti MS, Patel Y, Duffy PG, Cuckow PM, Wilcox DT, Mushtaq I. An initial experience of 100 paediatric laparoscopic nephrectomies with transperitoneal or posterior prone retroperitoneoscopic approach. Pediatr Surg Int 2007;23(8):795–9.
65. Gundeti MS, Taghizaedh A, Mushtaq I. Bilateral synchronous posterior prone retroperitoneoscopic nephrectomy with simultaneous peritoneal dialysis: a new management for end-stage renal disease in children. BJU Int 2007;99(4):904–6.
66. Martinez Urrutia MJ, Olivares Arnal P, Lopez Pereira P, Lobato Romera R, Alonso Melgar A, Jaureguizar Monereo E. Bilateral laparoscopic nephrectomy with simultaneous peritoneal dialysis catheter implantation. Pediatric transplantation 2007;11(2): 132–3.
67. Yucel S, Brown B, Bush NC, Ahmad N, Baker LA. What to anticipate with experience in pediatric laparoscopic ablative renal surgery. J Urol 2008;179(2):697–702; discussion
68. Kojima Y, Hayashi Y, Yasui T, Itoh Y, Maruyama T, Kohri K. Laparoscopic nephrectomy for a girl with giant hydronephrosis of a horseshoe kidney. Int J Urol 2007;14(7):647–9.
69. Harper JD, Shah SK, Baldwin DD, Moorhead JD. Laparoscopic nephrectomy for pediatric giant hydronephrosis. Urology 2007;70(1):153–6.
70. Cervellione RM, Gordon M, Hennayake S. Financial analysis of laparoscopic versus open nephrectomy in the pediatric age group. J Laparoendosc Adv Surg Tech A 2007;17(5):690–2.
71. Jordan GH, Winslow BH. Laparoscopically assisted continent catheterizable cutaneous appendicovesicostomy. J Endourol 1993;7(6):517–20.
72. Docimo SG, Moore RG, Adams J, Kavoussi LR. Laparoscopic bladder augmentation using stomach. Urology 1995;46(4):565–9.
73. Hedican SP, Schulam PG, Docimo SG. Laparoscopic assisted reconstructive surgery. J Urol 1999;161(1):267–70.
74. Cadeddu JA, Docimo SG. Laparoscopic-assisted continent stoma procedures: our new standard. Urology 1999;54(5):909–12.
75. Meng MV, Anwar HP, Elliott SP, Stoller ML. Pure laparoscopic enterocystoplasty. J Urol 2002;167(3):1386.
76. Elliott SP, Meng MV, Anwar HP, Stoller ML. Complete laparoscopic ileal cystoplasty. Urology 2002;59(6):939–43.
77. Casale P, Feng WC, Grady RW, Joyner BD, Lee RS, Mitchell ME. Intracorporeal laparoscopic appendicovesicostomy: a case report of a novel approach. J Urol 2004;171(5):1899.
78. Hsu TH, Shortliffe LD. Laparoscopic Mitrofanoff appendicovesicostomy. Urology 2004;64(4):802–4.
79. El-Feel A, Abdel-Hakim MA, Abouel-Fettouh H, Abdel-Hakim AM. Laparoscopic Augmentation Ileocystoplasty: Results and Outcome. Eur Urol 2008.
80. Shadpour P, Simforoosh N, Magsudi R, Shafee H. Totally laparoscopic combined freehand ileocystoplasty and Malone procedures. J Endourol 2005;19(4):471–5.
81. Lorenzo AJ, Cerveira J, Farhat WA. Pediatric laparoscopic ileal cystoplasty: complete intracorporeal surgical technique. Urology 2007;69(5):977–81.
82. Pedraza R, Weiser A, Franco I. Laparoscopic appendicovesicostomy (Mitrofanoff procedure) in a child using the da Vinci robotic system. J Urol 2004;171(4):1652–3.
83. Atala A, Kavoussi LR, Goldstein DS, Retik AB, Peters CA. Laparoscopic correction of vesicoureteral reflux. J Urol 1993;150(2 Pt 2):748–51.
84. McDougall EM, Urban DA, Kerbl K, et al. Laparoscopic repair of vesicoureteral reflux utilizing the Lich-Gregoir technique in the pig model. J Urol 1995;153(2): 497–500.
85. Baldwin DD, Pope JC, Alberts GL, et al. Simplified technique for laparoscopic extravesical ureteral reimplantation in the porcine model. J Endourol 2005;19(4):502–7.

86. Ehrlich RM, Gershman A, Fuchs G. Laparoscopic vesicoureteroplasty in children: initial case reports. Urology 1994;43(2):255–61.
87. Janetschek G, Radmayr C, Bartsch G. Laparoscopic ureteral anti-reflux plasty reimplantation. First clinical experience. Ann Urol (Paris) 1995;29(2):101–5.
88. Yeung CK, Sihoe JD, Borzi PA. Endoscopic cross-trigonal ureteral reimplantation under carbon dioxide bladder insufflation: a novel technique. J Endourol 2005;19(3):295–9.
89. Kutikov A, Guzzo TJ, Canter DJ, Casale P. Initial experience with laparoscopic transvesical ureteral reimplantation at the Children's Hospital of Philadelphia. J Urol 2006;176(5):2222–5; discussion 5–6.
90. Peters CA, Woo R. Intravesical robotically assisted bilateral ureteral reimplantation. J Endourol 2005;19(6):618–21; discussion 21–2.
91. Steeno OP. Varicocele in the adolescent. Adv Exp Med Biol 1991;286:295–321.
92. Szabo R, Kessler R. Hydrocele following internal spermatic vein ligation: a retrospective study and review of the literature. J Urol 1984;132(5):924–5.
93. Hagood PG, Mehan DJ, Worischeck JH, Andrus CH, Parra RO. Laparoscopic varicocelectomy: preliminary report of a new technique. J Urol 1992;147(1): 73–6.
94. Belloli G, Musi L, D'Agostino S. Laparoscopic surgery for adolescent varicocele: preliminary report on 80 patients. J Pediatr Surg 1996;31(11):1488–90.
95. Mischinger HJ, Colombo T, Rauchenwald M, et al. Laparoscopic procedure for varicocelectomy. Br J Urol 1994;74(1):112–6.
96. Matsuda T, Horii Y, Higashi S, Oishi K, Takeuchi H, Yoshida O. Laparoscopic varicocelectomy: a simple technique for clip ligation of the spermatic vessels. J Urol 1992;147(3):636–8.
97. Nyirady P, Pirot L, Altorjay A, et al. Laparoscopic varicocele operation: a chance to prevent the recurrence. Acta chirurgica Hungarica 1998;37(3–4):201–4.
98. Lynch WJ, Badenoch DF, McAnena OJ. Comparison of laparoscopic and open ligation of the testicular vein. Br J Urol 1993;72(5 Pt 2):796–8.
99. Dudai M, Sayfan J, Mesholam J, Sperber Y. Laparoscopic simultaneous ligation of internal and external spermatic veins for varicocele. J Urol 1995;153(3 Pt 1): 704–5.
100. Koyle MA, Oottamasathien S, Barqawi A, Rajimwale A, Furness PD, 3rd. Laparoscopic Palomo varicocele ligation in children and adolescents: results of 103 cases. J Urol 2004;172(4 Pt 2):1749–52; discussion 52.
101. Hirsch IH, Abdel-Meguid TA, Gomella LG. Postsurgical outcomes assessment following varicocele ligation: laparoscopic versus subinguinal approach. Urology 1998;51(5):810–5.
102. Kattan S. Incidence and pattern of varicocele recurrence after laparoscopic ligation of the internal spermatic vein with preservation of the testicular artery. Scand J Urol Nephrol 1998;32(5):335–40.
103. Ficarra V, Zanon G, D'Amico A, Mofferdin A, Tallarigo C, Malossini G. [Percutaneous, laparoscopic, and surgical treatment of idiopathic varicocele: analysis of costs]. Arch Ital Urol Androl 1998;70(2):57–64.
104. Riccabona M, Oswald J, Koen M, Lusuardi L, Radmayr C, Bartsch G. Optimizing the operative treatment of boys with varicocele: sequential comparison of 4 techniques. J Urol 2003;169(2):666–8.
105. Podkamenev VV, Stalmakhovich VN, Urkov PS, Solovjev AA, Iljin VP. Laparoscopic surgery for pediatric varicoceles: Randomized controlled trial. J Pediatr Surg 2002;37(5):727–9.
106. McManus MC, Barqawi A, Meacham RB, Furness PD, 3rd, Koyle MA. Laparoscopic varicocele ligation: are there advantages compared with the microscopic subinguinal approach? Urology 2004;64(2):357–60; discussion 60–1.
107. VanderBrink BA, Palmer LS, Gitlin J, Levitt SB, Franco I. Lymphatic-sparing laparoscopic varicocelectomy versus microscopic varicocelectomy: is there a difference? Urology 2007;70(6):1207–10.

108. Al-Hunayan A, Abdulhalim H, Kehinde EO, El-Barky E, Al-Awadi K, Al-Ateeqi A. Two-trocar laparoscopic varicocelectomy: cost-reduction surgical technique. Urology 2006;67(3):461–5.
109. Link BA, Kruska JD, Wong C, Kropp BP. Two trocar laparoscopic varicocelectomy: approach and outcomes. JSLS 2006;10(2):151–4.
110. Kaouk JH, Palmer JS. Single-port laparoscopic surgery: initial experience in children for varicocelectomy. BJU Int 2008.
111. Messina M, Zagordo L, Garzi A, et al. [Treatment of varicocele in pediatric age with retroperitoneoscopic "one trochar" technique. Long term follow-up]. Minerva urologica e nefrologica. Ital J Urol Nephrol 2006;58(1):81–6.

19 Genitourinary Tumors

Jonathan H. Ross

Abstract The management of pediatric genitourinary tumors has evolved in recent decades largely due to the efforts of multicenter trials. The respective roles of surgery, chemotherapy and radiation have been refined to optimize patient outcome and minimize patient morbidity. In the United States most Wilms tumors are managed by nephrectomy followed by chemotherapy, with radiotherapy added for patients with high stage or anaplastic tumors. The outcome for Wilms tumor is excellent. While some patients with neuroblastoma are managed with initial tumor resection, most have advanced disease and receive neoadjuvant treatment to allow more complete surgical excision of the tumor. Because these patients frequently have advanced disease, they are sicker at presentation and have a poorer outcome than children with Wilms tumor. Since most prepubertal testis tumors are benign, the initial surgical management is an excisional biopsy with frozen section. When a malignancy is found (almost always yolk sac tumor) the testis is removed. Most patients with yolk sac tumor have stage 1 disease and are managed with observation. Those who recur on observation and those who present with metastatic disease receive chemotherapy with excellent outcomes for all stages. The trend in the management of pelvic rhabdomyosarcomas has been to increase the utilization of neoadjuvant therapy in the hopes of minimizing the morbidity of the ultimate tumor resection. With this approach, most patients with vaginal tumors are cured without large resections and many with bladder and prostatic tumors are able to retain their bladders. However, many patients still require cystectomy either as part of the initial therapy or because of bladder deterioration due to the late effects of radiation. Patients with paratesticular rhabdomyosarcoma are managed with inguinal orchiectomy and chemotherapy. Older patients with stage 1 disease undergo a staging modified RPLND (as do patients with radiographic evidence of retroperitoneal involvement regardless of age). Abdominal radiation is added for patients with retroperitoneal disease.

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RENAL TUMORS

Wilms Tumor

Since its description by Wilms in 1899, the history of this renal tumor has represented one of the success stories of pediatric oncology. With optimal surgical techniques the survival of Wilms tumor was at best 20% in the early 20th century. The advent of radiation therapy led to survivals as high as 50%. And, with the addition of chemotherapy to the aremamentarium, survival rates of better than 90% are currently achieved (*1*). Large multicenter trials, notably the Children's Oncology Group (COG) in the United States and the International Society of Pediatric Oncology (SIOP) in Europe, continue to modify protocols in order to reduce the toxicity of therapy for those with favorable disease while continuing to improve the survival for those few groups of patients with a poor prognosis despite modern therapy.

Wilms tumor is the most common genitourinary malignancy of childhood. It is bilateral in approximately 5% of cases and multifocal in 12% of patients (*2*). It typically affects young children with a mean age of presentation of 3 years. Nearly all Wilms tumors occur sporadically with only 1–2% occurring in a directly inherited pattern. Several genes have been described to be associated with Wilms tumor including two genes on chromosome 11. Wilms tumor gene 1 (WT1) is a tumor suppressor gene at locus 11P13 and Wilms tumor gene 2 (WT2) is an insulin-like growth factor gene located at locus 11P15 (*3*, *4*). Several syndromes are associated with Wilms tumor. The most commonly described syndrome is the Beckwith Wiedemann syndrome, which consists of gigantism, macroglossia, abdominal wall defects, and hemihypertrophy. Wilms tumor has also been described in association with the WAGR syndrome (Wilms tumor, aniridia, genitourinary anomalies, and mental retardation) and the Denys-Drash syndrome (pseudohermaphroditism and glomerular disease). Patients with these syndromes should be placed on ultrasound screening protocols for abdominal tumors in the hopes of detecting the tumor at a lower stage (*5*). An ultrasound every 3 months until 6 or 7 years of age is usually recommended.

Most patients with Wilms tumor have a favorable classic triphasic histology. These tumors are composed of a blastemal component with nests of small blue cells, an epithelial component with pseudo-tubule formation, and a pink stromal component. Unfavorable histology is reflected in an anaplastic histological pattern which may be focal or diffuse. Along with stage, the presence of anaplasia is a powerful prognostic indicator. Fortunately, unfavorable histology occurs in only about 5% of cases.

Most children with Wilms tumor present with an abdominal mass noted by a family member or physician. Typically Wilms tumor patients appear

well at presentation with few if any symptoms. Occasionally they may present with decreased appetite or discomfort related to the abdominal mass. Rarely they may present with symptoms related to tumor bleeding, metastases, or a caval thrombus. The initial evaluation in most children with an abdominal mass is an ultrasound. Ultrasound can easily distinguish a solid mass from other masses such as hydronephrosis and can usually localize the mass to the kidney. Ultrasound is also very effective at evaluating the renal vein and vena cava for tumor thrombus. But computerized tomography scanning (CT) is the standard method for anatomic evaluation of the tumor and metastatic disease. On CT Wilms tumors are typically large heterogeneous masses arising from the kidney. Retroperitoneal lymphadenopathy, hepatic metastases, and other intraabdominal involvement with tumor can be evaluated with CT. Extending the CT into the chest allows identification of pulmonary metastases – the most common site for hematogenous spread. Magnetic resonance imaging (MRI) is occasionally employed, particularly in cases of venous involvement or when the CT cannot determine definitively that the tumor arises from the kidney. Other metastatic sites, such as bone and brain, are very rare and are evaluated only if signs or symptoms of there involvement are evident. In addition to routine blood chemistries, patients with Wilms tumor should be screened for coagulopathies as 25% will have abnormal clotting (*6*).

Staging of Wilms tumor is an important prognostic factor that guides adjuvant therapy. Staging is based on radiographic and surgical evaluation. The National Wilms Tumor Study/COG staging system is shown in the Table 19.1. In the United States most Wilms tumors are treated initially with nephrectomy. A transperitoneal approach is employed and abdominal exploration is undertaken. Historically a complete mobilization and exploration of the contralateral kidney was undertaken to rule out bilateral disease. However, with modern imaging, this step is no longer necessary (*7*). Sampling of the retroperitoneal lymph nodes remains a critical part of the operation. It has been demonstrated that a surgeon's impression of lymph node involvement

Table 19.1
Wilms tumor staging

Stage I	Tumor is limited to the kidney and completely excised
Stage II	Tumor extends through the renal capsule or into the renal sinus and is completely excised or previous biopsy
Stage III	Residual local disease including a positive margin, regional lymph node involvement, peritoneal tumor implants, preoperative tumor rupture or intraoperative tumor spill
Stage IV	Hematogenous metastases or extra-regional lymph node involvement

is inaccurate (*8*); failure to perform lymph node sampling has been shown to lead to under-staging and under-treatment of some patients (*9*). The nephrectomy is performed as a standard radical nephrectomy remaining outside Gerota's fascia and obtaining early control of the renal vessels when possible. Ipsilateral adrenalectomy is frequently performed, but if the upper pole of the kidney is uninvolved with tumor, and the adrenal can be safely dissected off of the kidney, then it may be spared.

While under the NWTS/COG protocols the therapy for most Wilms tumors begins with a nephrectomy, preoperative therapy is employed for patients with suprahepatic caval tumor thrombus, unresectable tumors, or bilateral tumors. For patients with caval tumor thrombus, pre-operative therapy will lead to thrombus shrinkage in 75% of cases and complete resolution in 25% of patients (*10*). For patients with suprahepatic caval thrombus, preoperative treatment allows avoidance of an otherwise necessary median sternotomy in 70% of patients. Therefore, the NWTS protocols have recommended preoperative therapy for these high-level thrombi. Pre-nephrectomy treatment is obviously appropriate for unresectable tumors. This determination should generally be made intra-operatively as radiographic studies may overestimate the extent of local disease. However, if complete tumor resection would require significant excision of normal abdominal organs such as liver or bowel, then complete excision should be deferred and pre-nephrectomy chemotherapy should be administered. The most common indication for pre-operative chemotherapy is the presence of bilateral disease. The goal in these cases is to maximize nephron-sparing without compromising oncological control. Generally, chemotherapy is given for 4–6 weeks and then the patient is re-assessed. If there is a good response, then chemotherapy may be continued for another 4–6 weeks at which time surgical exploration should be undertaken. If the tumors can be excised while leaving at least 2/3 of one kidney, then definitive extirpation should be undertaken. However, if this is still not possible, then consideration is given to simply biopsying the tumor and administering further treatment before definitive surgery. Even with this approach, some patients may ultimately require bilateral nephrectomies. Patients found to have anaplastic tumor(s) on biopsy should undergo earlier more aggressive surgical management. This overall approach to bilateral tumors may also be employed in patients with a solitary kidney and those at high risk for metachronous contralateral disease, such as those with hemihypertrophy or other pre-disposing syndromes.

Under the SIOP protocols in Europe, virtually all patients receive preoperative chemotherapy. The rationale is that pre-operative chemotherapy reduces intra-operative tumor spillage and overall complications (particularly hemorrhage). It also results in overall lower stage disease at the time of surgery, which may mitigate the need for more extensive adjuvant therapy such as radiation (*11*, *12*). On the other hand, pre-operative chemotherapy makes the histopathological evaluation of the tumor more difficult. It

may also artificially down-stage tumors leading to an inappropriate decrease in the intensity of therapy. Finally, occasional tumors may progress on chemotherapy making definitive treatment even more difficult. In the end, the overall survival rates in the NWTS and SIOP studies have been comparable, so either approach is reasonable (*13*).

Most patients in the United States undergo a radical nephrectomy as the first step in treatment followed by adjuvant therapy with chemotherapy for all patients and radiation therapy for patients with more aggressive tumors. Using these protocols, the NWTS has achieved overall survival rates for patients with favorable histology tumors ranging from 90% for stage IV tumors to 96% for stage I tumors (*1*, *14*, *15*). Patients with unfavorable histology tumors, particularly of higher stages have not fared as well with survivals of 91, 70, 56, and 17% for stages I, II, III, and IV unfavorable histology tumors, respectively (See Table 19.2).

Table 19.2
What every urologist should know about Wilms tumor

1. In the United States most patients undergo radical nephrectomy and lymph node sampling followed by adjuvant therapy. All patients receive chemotherapy and radiation is added for high stage or anaplastic tumors.
2. Pre-operative chemotherapy is employed in the United States for patients with unresectable tumors, patients with suprahepatic caval thrombus, and patients with bilateral disease. In Europe all patients receive pre-operative chemotherapy.
3. The most important prognostic factors are stage and histology.
4. Most patients with Wilms tumor have an excellent prognosis.

Other Renal Tumors

Wilms tumor is by far the most common renal tumor of childhood. Other malignant tumors affecting the kidney include clear cell sarcoma, malignant rhabdoid tumor, and renal cell carcinoma. Clear cell sarcoma differs from Wilms tumor clinically in its tendency to metastasize to bone. While aggressive adjuvant therapy is required for this tumor, recent studies have achieved good overall survivals. Malignant rhabdoid tumor continues to carry a poor prognosis even with aggressive therapy. Renal cell carcinoma occurs rarely in children. While it responds poorly to adjuvant therapy, survival in the presence of lymph node metastases is better for children than for adults. While clear cell sarcomas and malignant rhabdoid tumors are treated with chemotherapy and radiation, the management of renal cell carcinoma remains primarily surgical with immunotherapy a consideration for patients with metastatic disease.

ADRENAL TUMORS

Neuroblastoma

Neuroblastoma is the most common extracranial solid tumor of childhood. It arises from neural crest tissues and is composed of sheets of small blue cells often with pseudorosettes. Neuroblastoma typically occurs in infants and young children – with 75% of patients being younger than 4 years old (*16*). A mature form – ganlioneuroma – occurs in older children. Ganglioneuromas consist of ganglion cells, Schwann cells and collagen and are benign. They typically arise in the mediastinum and retroperitoneum – rarely in the adrenal gland. An intermediate lesion – ganglioneuroblastoma – contains features of both tumors and can follow a malignant course. Neurblastomas arise from the adrenal gland in 50% of cases. They can also arise from other areas of neural crest tissue, particularly along the sympathetic chain in the retroperitoneum.

Unlike Wilms tumor patients, children with neuroblastoma typically appear ill at presentation. They may suffer abdominal pain, weight loss, anemia, bone pain, or proptosis or periorbital ecchymoses. A palpable abdominal mass is often present. Neuroblastoma also has a wider range of common metastatic sites than Wilms tumor, including lymph nodes, bone marrow, cortical bone, liver, and skin. While CT is often the initial mode of evaluation, MRI can be particularly helpful in evaluating neuroblastoma due to the tumor's tendency to cross the midline in the retroperitoneum. Compared to CT, MRI can better delineate the relationship of the tumor to the great vessels and other retroperitoneal structures. The metastatic evaluation consists of a bone scan, skeletal survey, bone marrow biopsy and aspiration, and chest CT. A 24-h urine sample for homovanillic acid (HMA) and vanillylmandelic acid (VMA) is collected. Ninety to 95% of patients will have elevated levels of one or both chemicals in the urine (*17*).

Staging for neuroblastoma is less uniform than for Wilms tumor, but most systems are based on similar factors. In the International Neuroblastoma Staging System, tumors are generally considered to be stage 1 if there is complete gross excision with no lymphatic or hematogenous metastases (*18*). Stage 2 tumors are those with gross residual disease after resection and/or positive ipsilateral lymph nodes. Stage 3 tumors are unresectable tumors that extend beyond the midline or resectable tumors with positive contralateral lymph nodes. Any tumor with distant lymphatic or hematogenous metastases is designated stage 4. A special case of metastatic disease occurs in infants with a locally stage 1 or 2 tumor and metastases limited to the ipsilateral lymph nodes, liver, skin, and/or bone marrow. These stage 4S tumors typically resolve spontaneously without treatment. Aside from stage, poor prognostic signs for neuroblastoma include age greater than 1 year, unfavorable histology, and high amplification of the N-myc oncogene.

Treatment for neuroblastoma involves some combination of surgical excision, chemotherapy, and radiation therapy. To determine treatment, patients

are assigned to risk groups based on stage, histology, and the other prognostic factors. Those with low risk disease (a small percentage of patients) may be cured with surgical excision alone. Patients in intermediate and high risk groups usually undergo surgical staging, followed by multiagent chemotherapy in the hopes of ultimately being able to perform a more complete resection more safely. Patients in very high risk groups require intensive therapy and should be considered for more experimental therapies such as bone marrow transplantation. Radiation therapy, while unproven, may offer some benefit in local tumor control following partial resection of bulky tumors. Patients with 4S disease are usually cured with resection alone and may even be followed without resection as spontaneous regression is the rule. Some may require low dose chemotherapy or radiation to treat hepatomegaly that is compromising respiratory function. A small percentage of patients with 4S disease have unfavorable biological markers and may require more aggressive therapy. Neuroblastoma is increasingly being diagnosed prenatally. Similar to the 4S tumors diagnosed after birth, many prenatally detected adrenal masses will spontaneously regress (*19*) and some may be followed expectantly. Unfortunately, most patients with neuroblastoma have metastases at the time of diagnosis resulting in a poor overall prognosis for this disease (See Table 19.3).

Table 19.3
What every urologist should know about neuroblastoma

1. Children with neuroblastoma typically appear ill at presentation and most have metastatic disease.
2. Most patients with neuroblastoma will undergo staging and chemotherapy followed by tumor resection. A minority of patients will present with low-stage disease and may be treated with resection alone.
3. Neuroblastomas presenting prenatally or in infancy with specific metastatic disease may regress spontaneously and require no formal therapy.
4. The outlook for neuroblastoma is often poor, largely due to the high incidence of advanced disease at presentation.

Other Adrenal Tumors of Childhood

Other adrenal tumors that can be seen in childhood include adrenocortical carcinoma and pheochromocytoma. Both tend to occur in older children and adolescents. Adrenocortical carcinoma often presents with signs related to steroid hormone production such as Cushingoid features or virilization. As in adults, treatment is by surgical excision as these tumors cannot be cured with adjuvant therapy. The prognosis is somewhat better in children than adults, perhaps because the signs, such as virilization, are evident sooner leading to earlier diagnosis and treatment. The behavior of

pheochromocytomas in children is similar to that in adults. However, some studies suggest that malignancy may be rarer in children and multicentricity more common.

TESTICULAR TUMORS

Historically, pediatric testis tumors were treated in the same way as their adult counterparts. However, pediatric tumors are distinct epidemiologically, histopathologically, and in their clinical behavior. Epidemiologically, there is a bimodal age distribution of testicular tumors with a large peak in young adulthood and a second, smaller peak in young children. While the vast majority of testis tumors in adults are malignant with mixed germ cell tumors and seminomas predominating, many, if not most pediatric testis tumors, are benign with teratomas and yolk sac tumors predominating (*20*). These differences have led to a divergence in the management of testis tumors in children and adults.

Presentation and Evaluation

As in adults, testis tumors in children usually present as a palpable mass. Occasionally a reactive hydrocele may be present obscuring the mass on palpation. Therefore, any patient presenting with an acute or sub-acute hydrocele and an impalpable testis should undergo a scrotal ultrasound. An ultrasound is also helpful in distinguishing testicular from extratesticular lesions. Most extratesticular lesions are cystic and benign (e.g., epididymal cysts). However solid extratesticular lesions may represent neoplasms including paratesticular rhabdomyosarcoma. While the ultrasonographic characteristics of specific testicular tumors have been described, the findings are not specific enough to allow a definitive diagnosis on that basis alone. Once a testis tumor is confirmed by physical examination or ultrasonography, further radiological examination is usually deferred until after the histologic diagnosis is made. However, in cases where the pre-operative evaluation suggests a likely malignancy, a CT of the chest, abdomen, and pelvis is appropriate to evaluate for metastatic disease. As in adults, the most common metastatic sites are the retroperitoneum and lungs.

As in adults, testis tumor markers play an important role in the evaluation of pediatric patients. However, mixed germ cell tumors are vanishingly rare in prepubertal patients in whom nearly all malignant tumors are pure yolk sac tumors. For that reason, alphafetoprotein (AFP) is a helpful marker, whereas beta human chorionic gonadotropin (HCG) is not. AFP levels are elevated in 80–90% of patients with yolk sac tumor. In evaluating AFP levels it is important to keep in mind that AFP levels are normally quite high in infancy, measuring in the tens of thousands of ng/ml at birth. The level drops to several hundred ng/ml by 2 months of age, but does not reliably attain “normal” levels until 8–12 months of age (*21*). The half-life for AFP is approximately 5 days.

Surgical Approach

Historically the initial treatment for a pediatric testis tumor was an inguinal orchiectomy. This was based on the fact that the overwhelming majority of testis tumors in adults are malignant. However, recent studies have shown that a large percentage of prepubertal testis tumors are benign. Indeed some studies have shown that the large majority of childhood testis tumors are benign. Furthermore, most patients with a malignant tumor will have an elevated AFP since nearly all malignant tumors in children are pure yolk sac tumors. Therefore, in a child with a testis tumor and a normal AFP (keeping in mind the normal elevation of AFP in infants), the overwhelming likelihood is that the tumor is benign. There is growing evidence that these benign tumors can be safely managed with a testis-sparing approach and that testicles undergoing tumor excision grow well following simple tumor excision (*22*). Therefore the initial management of a testis tumor in the face of an age-appropriately normal serum AFP is an inguinal exploration with excisional biopsy. Through an inguinal incision the spermatic cord is controlled and softly occluded near the internal ring. The testis is then dissected and delivered into the inguinal incision within the tunica vaginalis. The testis is draped off and the tunica vaginalis is opened. The tumor is excised and sent for frozen section. If a benign tumor is confirmed, then the testis is closed with absorbable sutures and returned to the scrotum. If the biopsy demonstrates a malignancy or is equivocal, then an inguinal orchiectomy with high ligation of the spermatic cord should be performed. In assessing the frozen section it should be kept in mind that prepubertal teratomas are universally benign. In patients with a clearly elevated AFP for age, and in post-pubertal patients, an inguinal orchiectomy is appropriate. Once the tumor is excised, further evaluation and treatment will depend on the histology of the tumor.

Adjuvant Therapy

Germ Cell Tumors

Teratoma is probably the most common prepubertal testis tumor and is universally benign in these patients. If the final pathology confirms a teratoma in a prepubertal testis, then no further evaluation or treatment is necessary. Long-term follow-up of the remnant testis is reasonable to assess for growth at puberty. Epidermoid cysts are also benign and require no further treatment.

Yolk sac tumor represents the most common malignant testis tumor in children. Patients with yolk sac tumor should undergo a metastatic evaluation consisting of a CT scan of the chest, abdomen, and pelvis and serial serum AFP measurements. Patients with a negative radiographic evaluation and an appropriate decline in serum AFP levels following orchiectomy have stage 1 disease. Roughly 80% of patients will have stage 1 disease and may be managed with observation including periodic physical examination, CT scan and chest X-ray. Several large multicenter trials have demonstrated a

recurrence rate of approximately 15% for these patients, all of whom can be salvaged with 3–4 cycles of platinum-based multiagent chemotherapy (*23*–*28*). For the 20% of prepubertal yolk sac tumor patients who present with metastatic disease or a persistent elevation of serum AFP levels, multiagent platinum-based chemotherapy will cure 98%. Radiation therapy plays virtually no role in the management of these patients.

The role of retroperitoneal lymph node dissection (RPLND) is limited in children with yolk sac tumor. Most patients will have stage 1 disease. And, in contrast to adults, only a minority of those with metastatic disease will have metastases limited to the retroperitoneum (*29*). Furthermore, since stage 1 patients who recur on observation can be cured with the same chemotherapy regimen used for those presenting with metastatic disease, staging RPLND is of no practical value. Retroperitoneal surgery is indicated for staging in patients with equivocal nodes and normal tumor markers, and for those patients who, following treatment, have a residual retroperitoneal mass in the face of a normal AFP level. These are both rare circumstances.

Unlike prepubertal boys, adolescents typically have the same range of germ cell tumors as adults with embryonal and mixed germ cell tumors predominating. While there is limited data regarding the best management for adolescents, it seems reasonable to apply the same strategies as adults, employing observation, RPLND and/or chemotherapy depending on the specific histology and stage of disease. While teratomas are virtually always benign in prepubertal patients, they can be malignant in adults. Therefore, adolescents with teratoma should undergo an inguinal orchiectomy with appropriate metastatic evaluation and follow-up.

Stromal Tumors

Stromal tumors are rare in children and their behavior differs somewhat from that of their adult counterparts (*30*). Leydig cell tumors and juvenile granulosa cell tumors are universally benign in children and require no metastatic evaluation or adjuvant therapy. While approximately 10% of adult Sertoli cell tumors are malignant, malignancy is rare in older children and unreported in children under 5 years of age. Metastatic evaluation should be considered in older children and is probably prudent in infants and young children if worrisome histologic features are present such as cellular atypia or increased mitotic activity. Large cell calcifying Sertoli cell tumors are clinically and histologically distinct from standard Sertoli cell tumors. They are universally benign in children and require no metastatic evaluation. However, they are commonly associated with Carney's syndrome and Peutz-Jeghers syndrome. Children with large cell calcifying Sertoli cell tumors and their first-degree relatives should be evaluated for the stigmata of these syndromes. Some stromal tumors present with a mixed or undifferentiated histology. Most of these are benign, but there have been reports of metastatic disease in some, particularly in the presence of local invasion or malignant

histological characteristics. When malignant, these tumors can be particularly aggressive and combination treatment with RPLND, chemotherapy, and radiation may be required.

Gonadoblastoma

Gonadoblastomas contain both germ cell and stromal elements. They occur almost exclusively in dysgenetic gonads in patients with at least some Y chromatin in their karyotype. Gonadoblastomas occur in 3% of patients with true hermaphroditism and 10–30% of patients with mixed gonadal dysgenesis or pure gonadal dysgenesis and a 46 XY karyotype (*31*, *32*). They also occur commonly in the dysgenetic testis syndrome. While gonadoblastomas are benign, they can undergo malignant degeneration into seminoma/dysgerminoma. Gonadoblastomas are treated by orchiectomy. Indeed, any patient with a dysgenetic gonad and Y chromatin in his/her karyotype should undergo prophylactic gonadectomy in young childhood before malignant degeneration occurs. When malignant elements are present, a metastatic evaluation should be undertaken. These tumors are usually radiosensitive and, even in the face of metastatic disease, the prognosis is reasonably favorable (See Table 19.4).

Table 19.4
What every urologist should know about prepubertal testis tumors

1.	A majority are benign, including teratoma.
2.	Serum AFP is “elevated” in normal infants.
3.	Except in children over 1 year old with an elevated AFP, the operation should start with an excisional biopsy if feasible.
4.	Most patients are observed, and those with metastases are treated with chemotherapy and do well

RHABODOMYOSARCOMA

Rhabdomyosarcomas are soft tissue tumors arising from smooth muscle made up of small blue tumor cells. They occur in three primary histological patterns – embryonal, alveolar, and undifferentiated or anaplastic. The embryonal histology, the most common histology of genitourinary tumors, may manifest itself as a solid tumor or in a botryoid form.

Rhabdomyosarcomas occur throughout the body. Approximately 20% involve the genitourinary tract including the vagina, uterus, bladder, prostate, and paratesticular locations (*33*). The age distribution of these tumors is bimodal with a peak in the first 2 years of life and a smaller peak during adolescence (*34*). Prognosis is based on stage, histology, location of the tumor, and patient age. The botryoid form has a better prognosis than the embryonal

form. The alveolar tumors are the least favorable. Vaginal and paratesticular tumors have a generally better outlook than those occurring in the bladder and prostate. Infants less than 1 year old and children over 10 years of age fare less well than children between those ages (*35*). Evaluation of the primary tumor and metastases includes a chest X-ray, chest CT, CT or MRI of the primary site, bone scan, and bone marrow biopsy and/or aspiration.

Vaginal/Uterine Rhabdomyosarcoma

Vaginal rhadomysarcomas may be cured with chemotherapy alone. A biopsy is usually obtained which may be performed endoscopically for tumors high in the vaginal vault. Cystoscopy is also performed to rule out bladder invasion through the vaginovesical septum. Patients are then treated with multiagent chemotherapy. Re-evaluation is then undertaken with re-biopsy of any suspicious areas. Persistent disease, which occurs in a minority of patients, may be treated with radiation therapy or resection by partial vaginectomy or, rarely, vaginohysterectomy. Management of uterine rhabdomyosarcoma is similar to that for vaginal tumors. The initial biopsy can usually be made through dilation and curettage.

Bladder/Prostate Rhabdomyosarcoma

Bladder and prostate rhabdomyosarcomas may present with an abdominal mass, hematuria, or obstructive voiding symptoms. A digital rectal exam is important in the evaluation of any child presenting with urinary hesitancy, a decreased stream, or urinary retention. Historically the management of these tumors has included aggressive surgical resection with urinary diversion. In recent decades, efforts have been made to employ multimodal approaches with a strategy of bladder and prostate salvage. However, enthusiasm for this approach must be tempered by an increased risk of tumor recurrence and the possibility that a "salvaged" bladder may ultimately fail due to secondary effects of treatment, particularly radiation. Nonetheless, the initial surgical management for these tumors is a biopsy except in rare instances where tumor size and location are amenable to a partial cystectomy. The biopsy may be obtained endoscopically or in an open fashion. While percutaneous biopsies should be avoided when possible, for some prostatic tumors that cannot be approached endoscopically, a transrectal approach may be employed.

Once the diagnosis is confirmed and a metastatic evaluation completed patients are treated with multiagent chemotherapy. Following neoadjuvant therapy, definitive surgical intervention is undertaken. In many cases a partial cystectomy or a prostatectomy may be performed. However, some patients still require a formal cystoprostatectomy with urinary diversion. Patients then receive additional chemotherapy and, if margins are positive, radiation therapy as well.

With the modern emphasis on bladder salvage, 60% of patients in International Rhabdomyosarcoma Study (IRS)-III were alive with a functional intact bladder compared to only 20–25% of patients in IRS-I and IRS-II (*36*). However, there is little long-term data and deterioration in bladder function due to radiation can occurs years or decades following therapy. Indeed, in IRS-IV where there was longer follow-up and stricter criteria for "normal bladder function," only about 40% of patients were long-term survivors with a normal bladder (*37*). Of those patients undergoing partial cystectomy in IRS-IV as either initial therapy or following neo-adjuvant therapy, 12% died of disease, 6% developed secondary malignancies, 10% ultimately required a urinary diversion, and 16% have significant bladder dysfunction. Therefore, patients with retained bladders who undergo radiation therapy require life-long follow-up of bladder function. Consideration may also be given to excluding radiation therapy for select patients with favorable disease to prevent long-term bladder deterioration. The overall 4-year survival for pelvic rhabdomyosarcoma in IRS-III exceeded 85% (*36*).

Paratesticular Rhabdomyosarcoma

Paratesticular rhabdomyosarcomas usually present with an enlarging painless scrotal mass. By the time of presentation distinction from a primary testis tumor is usually not possible on physical exam, but can be seen with ultrasound. Some patients will present earlier with a palpable scrotal mass separate from the testis. While most extratesticular masses are benign, a solid extratesticular mass should be excised because of the risk of malignancy. This is particularly true if the mass is growing.

The initial management for paratesticular rhabdomyosarcomas is an inguinal orchiectomy. Trans-scrotal biopsies of solid scrotal masses should be avoided due to the risk of seeding of the incision if the mass is indeed a rhabdomyosarcoma. The orchiectomy should be performed just as for a testicular malignancy with early control of the spermatic vessels, mobilization of the testis outside of the tunica vaginalis, and orchiecomy en bloc with the spermatic cord ligated high in the inguinal canal. A permanent suture should be used to ligate the cord so that it may be identified if an RPLND is required.

The metastatic evaluation for paratesticular rhabdomyosarcoma includes a CT of the chest abdomen and pelvis. A majority of patients will have stage1 disease (*38*). The most common sites of metastases are the retroperitoneum and lungs. Patients with retroperitoneal metastases should undergo a modified unilateral nerve-sparing RPLND. Patients over 10 years of age without evidence of retroperitoneal disease should also undergo a staging RPLND. Younger children with a normal abdominal CT may be treated without an RPLND. Generally, patients with stage 1 disease receive multiagent chemotherapy. Abdominal radiation is added for those with retroperitoneal

Table 19.5
What every urologist should know about genitourinary rhabdomyosarcoma

1. Vaginal rhabdomyosarcomas are treated with a biopsy or limited resection followed by chemotherapy. A minority will ultimately require aggressive surgical resection.
2. Rhabodmyosarcomas of the bladder/prostate are usually managed with a biopsy followed by chemotherapy with/without radiation, and then definitive resection. Approximately half of patients will have an intact, functioning bladder at follow-up.
3. Paratesticular rhabdomyosarcomas are treated with inguinal orchiectomy followed by chemotherapy. Abdominal radiation is added for patients with retroperitoneal lymph node involvement. Clinical stage 1 patients over 10 years of age should undergo a staging RPLND.

involvement, even if an RPLND was performed. Overall survival rates for paratesticular rhabdomyosarcoma are approximately 90% (*38*) (See Table 19.5).

REFERENCES

1. Neville HL, Ritchey ML. Wilms' tumor: Overview of National Wilms' Tumor Study Group results. Urol Clin North Amer 2000;27:435–442.
2. Breslow N, Beckwith JB, Ciol M, Sharples K. Age distribution of Wilms' tumor; report from the National Wilms' Tumor Study. Cancer Res 1988;15:1653–1657.
3. Wagner KJ, Roberts SG. Transcriptional regulation by the Wilms' tumour suppressor protein WT1. Biochem Soc Trans 2004;32:932–935.
4. Ruteshouser EC, Huff V. Familial Wilms tumor. Amr J Med Genet 2004;129C:29–34.
5. Choyke PL, Siegel MJ, Craft AW, Green DM, DeBaun MR. Screening for Wilms tumor in children with Beckwith-Wiedemann syndrome or idiopathic hemihypertrophy. Med Pediatr Oncol 1999;32:196–200.
6. Leung RS, Liesner R, Brock P. Coagulopathy as a presenting feature of Wilms tumour. Eur J Pediatr 2004;163:369–373.
7. Ritchey ML, Shamberger RC, Hamilton T, Haase G, Argani P, Peterson S: Fate of bilateral renal lesions missed on preoperative imaging: a report from the National Wilms Tumor Study Group. J Urol 174:1519–1521, 2005
8. Othersen HB Jr, DeLorimer A, Hrabovsky E, et al. Surgical evaluation of lymph node metastases in Wilms' tumor. J Pediatr Surg 1990;25:330–331.
9. Shamberger RC, Guthrie KA, Ritchey ML, Haase GM, Takashima J, Beckwith JB, D'Angio GJ, Green DM, Breslow NE. Surgery-related factors and local recurrence of Wilms tumor in National Wilms Tumor Study 4. Ann Surg 1999;229:292–297.
10. Ritchey ML, Kelalis PP, Haase GM, et al. Preoperative therapy for intracaval and atrial extension of Wilms' tumor. Cancer 1993;71:4104–4110.
11. Lemerle J, Voute PA, Tournade MF, et al. Preoperative versus postoperative radiotherapy, single versus multiple courses of actinomycin D, in the treatment of Wilms' tumor : Preliminary results of a controlled clinical trial conducted by the International Society of Paediatric Oncology (SIOP). Cancer 1976;38:647–654.
12. Graf N, Tournade MF, de Kraker J. The role of preoperative chemotherapy in the management of Wilms' tumor. Urol Clin N Amer 2000;27:443–454.

13. Weirich A, Ludwig R, Graf N, Abel U, Leuschner I, Vujanic GM, Mehls O, Boos J, Beck J, Royer-Pokora B, Voute PA. Survival in nephroblastoma treated according to the trial and study SIOP-9/GPOH with respect to relapse and morbidity. Ann Oncol 2004;15:808–820.
14. Green DM, Breslow NE, Beckwith JB, Finkelstein JZ, Grundy PE, Patrick RM et al. Effect of duration of treatment on treatment outcome and cost of treatment for Wilms' tumor: A report from the National Wilms' Tumor Study Group. J Clin Oncol 1998;16:3744–3751.
15. Green DM, Beckwith JB, Breslow NE, Faria P, Moksness J, Finkelstein JZ et al. Treatment of children with stages II to IV anaplastic Wilms' tumor: a report from the National Wilms' Tumor Study Group. J Clin Oncol 1994;12:2126–2131.
16. Fortner J, Nicastri A, Murphy ML. Neuroblastoma: natural history and results of treating 133 cases. Ann Surg 1968;167:132–142.
17. Williams CM and Greer M. Homovanillic acid and vanillylmandelic acid in diagnosis of neuoblastoma. JAMA 1963;183:836–840.
18. Brodeur GM, Pritchard J, Berthold F, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. J Clin Oncol 1993;11: 1466–1477.
19. Yamamoto K. Handa R, Kikchi A, et al. Spontaneous regression of neuroblastoma detected by mass screening. J Clin Oncol 1998;16:1265–1269.
20. Pohl HG, Shukla AR, Metcalf PD, et al. Prepubertal testis tumors: actual prevalence rate ofhistological types. J Urol 2004;172:2370.
21. Grady R, Ross JH, Kay R. Epidemiologic features of teratomas of the testis in a prepubertal population. J Urol 1997;158:1191.
22. Valla JS. Testis-sparing surgery for benign testicular tumors in children. J Urol 2001;165:2280.
23. Haas RJ, Schmidt P, Gobel U, Harms D. Testicular germ cell tumors an update – results of the German Cooperative Studies 1982–1997. Klin Padiatr 1999;211:300.
24. Rogers PC, Olson TA, Cullen JW, et al. Treatment of children and adolescents with stage II testicular and stages I and II ovarian malignant germ cell tumors: A Pediatric Intergroup Study – Pediatric Oncology Group 9048 and Children's Cancer Group 8891. J Clin Oncol 2004;22:3563.
25. Cushing B, Giller R, Cullen JW, et al. Randomized comparison of combination chemotherapy with etoposide, bleomycin, and either high-dose or standard-dose cisplatin in children and adolescents with high-risk malignant germ cell tumors: a pediatric intergroup study – Pediatric Oncology Group 9049 and Children's Cancer Group 8882. J Clin Oncol 2004;22:2691.
26. Mann JR, Raafat F, Robinson K, et al. The United Kingdom Children's Cancer Study Group's second germ cell tumor study: carboplatin, etoposide, and bleomycin are effective treatment for children with malignant extracranial germ cell tumors, with acceptable toxicity. J Clin Oncol 2000;18:3809.
27. Lo Curto M, Lumia F, Alaggio R, et al. Malignant germ cell tumors in childhood: results of the first Italian cooperative study "TCG 91". Med Pediatr Oncol 2003;41:417.
28. Schlatter M, Rescorla F, Giller R, et al. Excellent outcome in patients with stage I germ cell tumors of the testes: a study of the Children's Cancer Group/Pediatric Oncology Group. J Pediatr Surg 2003;38:319.
29. Grady R, Ross JH, Kay R. Patterns of metastatic spread in prepubertal yolk sac tumor of the testis. J Urol 1994;153:1259.
30. Thomas JC, Ross JH, Kay R. Stromal testis tumors in children: a report from the prepubertal testis tumor registry. J Urol 2001;166:2338.
31. Savage MO, Lowe DG. Gonadal neoplasia and abnormal sexual differentiation. Clin Endocrinol 1990;32:519.
32. Ramani P, Yeung CK, Habeebu SSM. Testicular intratubular germ cell neoplasia in children and adolescents with intersex. Am J Surg Pathol 1993;17:1124
33. Crist WM, Anderson JR, Meza JL, et al. Intergroup rhabdomyosarcoma study-IV: results for patients with nonmetastatic disease. J Clin Oncol 2001;19:3091–3102.

34. La Quaglia M, Heller G, Ghavami F, et al. The effect of age at diagnosis on outcome in rhabdomyosarcoma. Cancer 1994;73:109–117.
35. Joshi D, Anderson JR, Paidas C, et al. Age is an independent prognostic factor in rhabdomyosarcoma: a report from the soft tissue sarcoma committee of the Children's Oncology Group. Pediatr Blood Cancer 2004;42:64–73.
36. Hays DM, Raney RB, Wharam MD, et al. Children with vesical rhabdomyosarcoma (RMS) treated by partial cystectomy with neoadjuvant chemotherapy, with or without radiotherapy. A report from the Intergroup Rhabdomyosarcoma Study (IRS) Committee. J Pediatr Hematol Oncol 1995;17:46–52.
37. Arndt C, Rodegerg D. Breitfeld PP, et al. Does bladder preservation (as a surgical principle) lead to retaining bladder function in bladder/prostate rhabdomyosarcoma? Results from the Intergroup Rhabdomyosarcoma Study Group IV. J Urol 2004;171:2396.
38. Wiener ES, Lawrence W, Hays D, et al. Retroperitoneal node biopsy in childhood paratesticular rhabdomyosarcoma. J Pediatr Surg 1994;29:171–178.

20 Genitourinary Trauma

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Abstract Pediatric genitourinary trauma is uncommon but harbors several important differences when compared to adult trauma. Although the fundamental principles apply for renal trauma, the urologist must appreciate the different clinical responses to trauma in children with respect to hemodynamic stability, presence of hematuria, and the increased likelihood of underlying congenital anomalies. Additionally, urologists must be aware that a severe pelvic injury may involve the bladder neck, with the potential for very poor outcomes and that early evaluation and surgical intervention may be required. Genital injuries in a child must always be concerning for abuse. The vast majority of pediatric genitourinary trauma is expected to have excellent long-term outcomes, and due diligence to its nuances will ensure that these children recover to their maximum potential.

Keywords Pediatric genitourinary trauma · Management of renal injury · Imaging for urinary trauma in children

INTRODUCTION

Pediatric genitourinary trauma is uncommon, but can account for substantial morbidity and mortality. The pediatric trauma patient differs from the adult with respect to both the diagnosis and treatment, and these nuances are emphasized here. Furthermore, with such an emphasis on conservative treatment in these patients, great care must be taken to understand the varied presentation, diagnosis, and treatment to ensure the best possible outcomes.

EPIDEMIOLOGY

Approximately 90% of genitourinary injuries are due to blunt trauma, and the majority of these arise from motor vehicle accidents, with only a small minority from recreational activities (*1*). It is uncommon for these injuries to

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occur in isolation, and retroperitoneal injuries can be associated with other life-threatening conditions (*2*). As per many areas in pediatric surgery, differences do occur when compared to adults, primarily with respect to hemodynamic stability and the consideration of congenital anomalies.

The majority of pediatric urologic injuries occur in the kidney, but the vast majority of these are managed conservatively (*2*). Penetrating injuries have a very high incidence of surgical management, and also have a high rate of collateral injuries (*3*).

RENAL INJURIES

The three major differences when dealing with pediatric renal injuries, in comparison to adults, involve the patient's tolerance of blood loss, the increased incidence of congenital anomalies, and the lower incidence of hematuria even with significant renal injury (*2*, *4–6*). Historically, it was believed that pediatric kidneys were more susceptible to traumatic injury than their adult counterparts. This was felt to be due to the lower position and increased mobility of the pediatric kidney within the retroperitoneum, increased elasticity of the rib cage, and weaker abdominal musculature. However, this has been difficult to demonstrate statistically (*4*).

Hemodynamic Stability

Quinlan and Gearhart first described the hemodynamic differences between adults and children following urologic trauma (*5*). It is a widely held belief that children are much more capable of maintaining a normal blood pressure in the face of significant blood loss. This has two main implications, namely that any treating physician must not rely on blood pressure as a means of triage, and also be wary of an increased heart rate in the setting of severe trauma. Secondly, the treatment algorithm applied to adults is primarily dependent upon blood pressure, and that may not be appropriate for the pediatric population. Santucci, with the Renal Trauma Subcommittee, addressed this issue with a comparison of pediatric and adult renal trauma and recommended that indications for imaging should not be different (*7*).

Congenital Anomalies

In the pediatric population, congenital anomalies are seen much more frequently in the setting of trauma. Preexisting renal anomalies are seen approximately 3–5 times more frequently than in the adult population (*4*, *7–9*). This is thought to be due to an increased susceptibility to hematuria in the presence of a ureteropelvic junction (UPJ), hydronephrosis, or pelvic location of the kidney (*10*). However, reviews by both Chopra and McAleer concluded that despite this, these injuries are most likely to be minor contusions and respond well to conservative treatment (*4*, *8*).

Hematuria

Finally, the incidence of hematuria is much less frequent in the pediatric patient, and this has significant implications with respect to screening (*2*, *6*). Studies have demonstrated that in renal injuries grade 2 and higher, up to 70% may not be associated with hematuria. These factors must be understood and applied to the pediatric patient as they may directly affect care and outcomes. Most importantly, in the pediatric patient, this dictates that the absence of hematuria does not exclude renal trauma, and subsequent imaging cannot be excluded based solely on the presence/absence of hematuria.

EVALUATION AND IMAGING

First and foremost, as with any trauma assessment, is an immediate triage including an assessment of airway, breathing, circulation, and neurologic disability. Rarely will any genitourinary trauma occur in isolation, and therefore any treating urologist must have a low threshold for involving the entire trauma team. Rapid resuscitation must occur, with large bore intravenous catheters and large volumes of isotonic crystalloid solutions.

The most importing staging parameter for renal trauma is the hemodynamic stability of the patient. Most patients will present with normal blood pressure and heart rate, and therefore are stable enough to undergo thorough history, including the mechanism of injury and physical examination (*11*, *12*). Children in whom shock is not immediately apparent require intense observation with regular monitoring of vital signs to ensure the patient does not suddenly decompensate (*13*). Initial investigations include a screening urine dipstick, complete blood count, crossmatch for potential blood transfusions, and radiographic imaging. However, in cases of hemodynamic instability, no time is wasted en route to definitive surgical intervention.

Despite the widespread use of indications for imaging in adults, it was not until very recently that Santucci et al. determined that these same criteria can be used in children (*7*). Indications for imaging include the following:

(1) Any intrabdominal penetrating trauma
(2) Any blunt trauma with a high probability of organ injury, i.e., significant deceleration or high velocity injury (motor vehicle, or pedestrian/bicycle versus motor vehicle accident), fall from >15 feet, or significant blow to abdomen or flank (e.g., bat, helmet)
(3) Trauma that has resulted in an associated injury with a high probability of involving the genitourinary system, as seen with a fracture of the thoracic ribs, spine, pelvis, or femur and bruising of the torso/perineum, or signs of peritonitis.
(4) Gross hematuria
(5) Microscopic hematuria (<50 red blood cells per high powered field) associated with shock (systolic blood pressure <90 mm Hg)

RADIOGRAPHIC IMAGING

CT Scan

CT scanning is the imaging modality of choice, as it allows for a comprehensive assessment of almost any organ system (*7*, *14*). The renal protocol consists of a non-enhanced, enhanced, and delayed phases, as this demonstrates renal vasculature, parenchyma, and collecting system (*15*–*17*). Helical and multidetector CT scanners offer significant advantages over conventional technique, as they offer thinner cuts and faster imaging speeds (*18*). The initial, arterial phase, occurs approximately 75 s after intravenous injection, which allows for the detection of arterial bleeding. Scans obtained during the urographic phase allow detection of injuries to the collecting system, and subtle parenchymal injuries. Delayed images (10–15 min after injection) are required to detect urinary contrast extravasation (*18*).

The most important advantage to CT is the prognostic value. The American Association for the Surgery of Trauma developed a grading scale which has been based on the depth of renal parenchymal injury, involvement of the collecting system, and injury to the vessels (*19*). The scale has been shown to correlate with the need for kidney repair or removal (*17*).

Grade 1
Hematuria with normal imaging studies.
Contusions.
Non-expanding subcapsular hematomas.

Grade 2
Non-expanding perinephric hematomas confined to the retroperitoneum.
Superficial cortical lacerations less than 1 cm in depth without collecting system injury.

Grade 3
Renal lacerations greater than 1 cm in depth that do not involve the collecting system.

Grade 4
Renal lacerations extending through the kidney into the collecting system.
Injuries involving the main renal artery or vein with contained hemorrhage.
Segmental infarctions without associated lacerations.

Grade 5
Shattered or devascularized kidney.
UPJ avulsions.
Complete laceration or thrombosis of the main renal artery or vein.

Ultrasound

The use of ultrasound in trauma remains controversial, especially with respect to renal and retroperitoneal injuries. It has been reported to detect

as few as 22% of renal injuries (*20*). However, it remains popular due to its effectiveness for a focused abdominal sonography for trauma (FAST). The images may show a parenchymal laceration, increased cortical echogenicity, or perinephric fluid. Doppler imaging can be a useful tool to demonstrate a renal artery occlusion (*20*).

Ivp

If hemodynamic instability precludes a thorough evaluation, a single shot IVP is performed on the operating room table 15 min after injecting 2 mg/kg of intravenous contrast to evaluate the function of the contralateral kidney (*16*). However, the patient's perfusion status may result in very poor quality images that may make definitive decisions difficult.

Retrograde Pyelogram

A retrograde pyelogram (RPG) can be very useful to determine if a complete UPJ disruption has occurred or in the case of an unresolving urinoma to determine if a retrograde stent will be useful. However, this is typically performed several days after the trauma, and not part of the initial management.

MANAGEMENT OF RENAL TRAUMA

The initial, fundamental determinant of treatment depends upon the hemodynamic stability of the patient. Once this status has been confirmed and initial resuscitation has begun, the staging on CT scan provides an excellent basis for further evaluation and management. As with most trauma literature, most of the literature has been reported on adults, but the same principles are applied to children (*11*, *14*, *21*–*23*).

All hemodynamically stable grade 1–3 injuries are managed conservatively, with excellent long-term outcomes (*2*, *23*–*25*). Grade 1 injuries account for about 80% of renal injuries, and in the absence of gross hematuria, the patient can be discharged the same day. Gross hematuria or grades 2–3 are admitted for at least 24 h, due to the concern of secondary bleeding. Once the gross hematuria has resolved, the child can be discharged. Fever is common and is likely due to the presence of a hematoma, and is unlikely due to an infectious cause. The child must avoid strenuous activity until imaging has documented complete healing (*2*, *24*). Once this has been documented, no further imaging is required, but the child must be followed annually through adulthood for hypertension (*13*).

Grade 4 and 5 injuries are much more likely to be associated with significant blood loss, hypotension, and other organ injuries; and therefore a much higher likelihood of operative intervention (*2*, *22*–*24*). Hemodynamic instability or significant penetrating injury mandates immediate surgical exploration. The contralateral kidney is assessed via intraoperative IVP if not staged accurately prior to surgery (*16*). Renal artery occlusion is more

common in pediatrics, as the increased mobility of the kidney results in sudden traction on the artery, an intimal tear, thrombosis, and occlusion.

The stable patient is admitted for bed rest and close observation, preferably in an intensive care setting. They are followed with serial bloodwork, as well as regular and frequent vital signs. Many authors advocate antibiotics if the patient has documented urinary extravasation, although definitive data demonstrating efficacy is lacking (*26*). Repeat renal imaging is required if there is any deterioration in the clinical scenario or as routine protocol at 48 h (*13*). After 48 h, without deterioration and follow-up CT scan to confirm stability of the hematoma or urinoma, CT confirmation of stability, the child can be transferred to the pediatric surgical ward where they remain on bed rest.

With the development of hypotension unresponsive to vigorous intravenous fluids or the requirement for more than 3 units of packed red blood cells, more aggressive intervention must be considered.

SURGICAL MANAGEMENT OF RENAL TRAUMA

Laparotomy

The hemodynamically unstable patient should undergo immediate surgery. Other indications for open surgical exploration include: a grade 3 injury undergoing laparotomy for other intraabdominal injury and/or expanding hematoma. In this scenario, expert opinion is that the kidney should be formally explored, repaired when possible, with drains and interposed omentum used to prevent the possibility of a fistula (*7*).

The standard incision is a midline, as this gives the best access to the major vessels. Vascular control is obtained before opening Gerota's fascia due to its tamponading effect and the potential for uncontrollable bleeding.

Renal repair and salvage requires complete mobilization and visualization of the kidney. All non-viable tissue is debrided and bleeding arterial vessels oversewn. Parenchymal defects can be closed primarily or with the interposition of Gelfoam, Surgicel, omentum, or perirenal fat. Collecting system injuries are only closed primarily if a tension free, watertight, closure is possible with well-vascularized tissue. If this is not possible double J stent or nephrostomy tube and drains are placed with perirenal drains also present to prevent gastrointestinal fistulas (*2*, *9*, *10*, *7*).

Nephrectomy may be necessary if the bleeding cannot otherwise be controlled, the damage is deemed irreparable, or to minimize operative time in the hypothermic, coagulopathic or multiple organ injured patient (*7*, *9*).

Endoscopic and Radiologic Intervention

Occasionally, a patient initially managed with observation will not respond to conservative management, but is not in an immediately life-threatening situation. The slow, but persistent drop in hemoglobin and the

expanding, symptomatic urinoma are two examples. In this situation, open surgical exploration carries a very high risk of significant blood loss and nephrectomy (*27*–*29*).

Renal angiography and angioembolization can be very useful for a slow, persistent bleed or a delayed bleed secondary to an acquired arteriovenous fistula (AVF) or pseudoaneurysm (*7*, *30*–*34*). This has been reported to have an 80% success rate at stopping any persistent bleeding, with treatment failure necessitating open surgical intervention.

Urinary extravasation is the most common complication of renal trauma (*35*), but only persists beyond a few days in 13–26% of patients (*22*, *35*, *36*). Although most are asymptomatic and diagnosed on follow-up imaging, the urinoma may be responsible for persistent pain, fever, or ileus (*26*). Many authors advocate varying combinations and timing of either retrograde stents, percutaneous drainage of the urinoma, or percutaneous nephrostomy tubes. There is not a proven gold standard, and therefore, care must be individualized.

Persistent urinary extravasation may be due to a necrotic polar parenchymal injury, which may require open surgical exploration and resection.

UPJ DISRUPTION

The complete disruption of the UPJ is a rare complication that follows a significant trauma, usually a rapid deceleration with associated injuries severe enough to mandate immediate laparotomy (*37*). Therefore, the patient is not fully evaluated prior to surgery, and the diagnosis is often delayed. Clinical suspicion arises from fever, flank pain, ileus, sepsis, or elevated creatinine. Diagnosis is delayed greater than 3 days in 50% of patients. Pathognomonic findings on triphasic CT include the following: (*1*) prompt function of the ipsilateral kidney; (*2*) no parenchymal injury but significant urinoma (often medial to the kidney); (*3*) non-visualization if the ureter on the delayed images (*4*, *8*).

Primary repair can be attempted if the injury has been discovered within 5 days. If not possible, urinary drainage with nephrostomy tube is preferable, until secondary repair can be performed 6–8 weeks after the injury. Pre-operative work-up requires DMSA to determine renal function, and antegrade and retrograde pyelograms to determine the length of the defect. Repair may require the surgeon's entire reconstructive armamentarium, with renal mobilization and primary re-anastomosis, ureteroureterostomy, ureterocalycostomy, ileal ureter, or autotransplant (*37*).

LONG-TERM COMPLICATIONS OF RENAL TRAUMA

Hypertension has been reported to occur in an average of 5% of significant renal injuries (*38*), but many series do not report any incidence (*26*). The fundamental pathophysiology involves segmental renal ischemia,

but this can be due to a Page kidney, a pseudoaneurysm, or renal artery stenosis. The incidence has been reported to not differ between surgically and conservatively managed patients (*39*). Transient hypertension can occur up to 50 days after injury, with spontaneous resolution. Chronic hypertension has been reported to occur as late as 32 years after renal injury (*38*, *40*, *41*). A very high incidence is seen after renal artery occlusion, up to 50% in several series (*42*, *43*). Segmental scarring is an uncommon cause of hypertension, but is readily treated with partial nephrectomy (*44*). Hypertension secondary to a small non-functioning kidney is cured with nephrectomy (*38*).

Delayed hematuria can be seen 6–8 weeks after the injury, and is likely due to a pseudoaneurysm or AVM. Diagnosis is confirmed with CT or MR angiography. DMSA scan is very useful to determine post-traumatic scarring or to confirm non-function after arterial occlusion. Super selective angiographic embolization is an effective treatment for both pseudoaneurysm and AVM.

URETERAL INJURY

A traumatic ureteric injury is a rare event, accounting for less than 1% of all genitourinary injuries, and is often associated with other life-threatening injuries (*45*, *46*). These are even rarer in children, as they are usually secondary to gunshot and stab wounds.

Most of these injuries are discovered at laparotomy, mandated by the severe penetrating injury (*47*). However, many are missed, which results in significantly worse outcomes. An injured ureter secondary to blunt abdominal trauma often results in a delayed diagnosis, as hematuria occurs in less than 1/3 of patients, and standard imaging is associated with a high false-negative rate (*47*).

In the case of the immediate diagnosis, treatment depends on location and severity of the injury, with the majority undergoing primary repair with stenting (*46*, *47*). A delay up to 5 days can still be successfully repaired with an open anastomosis. However, most patients with a more delayed diagnosis, in a University of Pennsylvania series, were managed with a percutaneous nephrostomy tube or endoscopic placement of stents (*47*, *48*).

Older series have shown very poor outcomes with delayed primary repair, with a nearly 50% nephrectomy rate (*49*).

Iatrogenic ureteric injuries are much less common in the pediatric population, but have been seen following large retroperitoneal resections, laparoscopic appendectomy, and laparoscopic orchiopexy (*10*). It has been reported that ureteric injury or avulsion occurs in less than 2% of pediatric ureteroscopies (*50*–*52*). These are usually very readily recognized and management of small perforations is very successful with an internal stent, while an avulsion will likely require an open repair with specifics determined by the location and extent of the injury (*50*–*52*).

BLADDER INJURIES

Bladder injuries are more common with blunt trauma, and are associated with pelvic fracture and significant abdominal injuries. The severity of the co morbid injuries is belied by the overall 20% mortality rate. Clinical suspicion is elevated whenever a pelvic fracture is encountered, and imaging is mandated when associated with gross hematuria or an inability to void. A perineal hematoma is also considered a relative indication for imaging.

Children are at a much higher risk of bladder injury after blunt trauma due to the tendency of a full bladder to be outside of the pelvis. Furthermore, pediatric patients are also more likely to suffer an injury across their bladder neck (*53*, *54*). This is an important injury to look for, as the simple placement of a suprapubic tube will not prevent a urinoma or osteomyelitis (*54*).

Rupture of a Bladder Augmentation

An often underappreciated, but potentially life-threatening, risk for bladder rupture is the presence of a bladder augmentation (*55*). Even the most minor injury (e.g., sledding, jumping on a trampoline, or minor contact during sports) can result in an anastomotic rupture and peritonitis (*56*). It cannot be emphasized strongly enough that patients with a bladder augmentation must be thoroughly evaluated with the smallest suspicion of rupture. Especially given that the majority of augmentations occur in the neurologically impaired, presentation and diagnosis can be delayed until the patient is septic and further delay in diagnosis can result in a significant risk of mortality (*55*, *56*). A significant leak, as seen on CT cystogram, or an unstable patient mandates immediate laparotomy, irrigation of the abdominal cavity, primary closure, and liberal use of peritoneal and intravesical drains (*56*). Neurosurgical consultation and consideration of externalizing the ventriculo-peritoneal shunt should be considered. Smaller leaks in the stable patient can be managed with percutaneous drainage of the urinoma and large bore catheter drainage of the augmentation (*55*, *56*).

IMAGING

Diagnosis requires a cystogram, either with conventional flouroscopy or CT, as CT with intravenous contrast is unlikely to distend the bladder sufficiently, even with occlusion of the foley catheter (*57*). However, a standard cystogram is less sensitive than CT, as the AP views will not detect a small posterior leak. In children it is important to ensure that the bladder is filled to a minimum of ½ expected capacity, as determined by age + 2 in ounces (×30 for cc) to a maximum of 300 cc (*10*).

TREATMENT

Once a bladder rupture has been diagnosed, it is important to differentiate between intra- and extraperitoneal ruptures. Extraperitoneal ruptures are twice as common, and may be managed with Foley catheter drainage, except the aforementioned bladder neck injuries, presence or suspicion of bony fragments within the laceration, or if management of the pelvic injury requires orthopedic hardware. The surgeon must remain wary of intraoperative complications, as dislodgment of the adjacent pelvic hematoma can result in significant bleeding. The catheter must be of sufficient bore to accommodate the expected bleeding and clots, and if this cannot be achieved via the urethra, a suprapubic catheter is recommended (*58*). After 7–10 days, cystogram is repeated to confirm healing and the catheter can be removed in the absence of extravasation. Antibiotics are required for the duration of catheterization and for 48 h after removal (*10*).

Intraperitoneal ruptures are usually much larger and require laparotomy and primary repair. It is very important to completely inspect the bladder and bladder neck to look for further lacerations and to ensure no herniation of intraperitoneal contents. Larger bore urethral or suprapubic catheters are placed as well as a perivesical drain.

Lacerations of the bladder neck require an intravesical repair in multiple layers. These can be devastating injuries, fraught with long-term complications. The ultimate management may require bladder neck closure to regain continence. The surgeon must also be aware of the high rate of associated anterior urethral injuries, mandating a urethrogram or urethroscopy (*54*).

URETHRAL INJURY

The immature boney pelvis and more intra-abdominal location of the bladder result in significant differences with respect to traumatic urethral injuries when pediatric patients are compared to adults. There are four unique aspects to pediatric urethral injuries that must be considered in all children with pelvic trauma (*10*, *53*, *54*, *59*, *60*):

(1) The associated pelvic fracture is more likely to be unstable and the prostatic urethra is likely to be severely dissociated or displaced.
(2) The higher risk of prostatic urethral displacement results in a much greater likelihood of a complete urethral disruption, compared to adult males.
(3) Concurrent bladder and bladder neck injuries occur in up to 20% of patients.
(4) Pre-pubertal females with pelvic fractures are approximately four times more likely to have urethral injuries.

For the male patient, this results in a much longer urethral defect for reconstruction, increasing the risks of erectile dysfunction and incontinence (*10*, *53*, *54*, *59*). In females, the risk of near total urethral loss is higher, necessitating closure of the bladder neck in some patients (*60*, *61*).

DIAGNOSIS

The diagnosis of pelvic trauma should immediately result in the suspicion of a urethral injury, with a low threshold for investigation. Urethral injuries may also result from penile, vaginal, or perineal trauma. Unfortunately, many injuries are iatrogenic, often due to the inflation of a Foley catheter balloon in the urethra. Absolute indications for investigation include

(1) blood at meatus combined with a perineal hematoma and the inability to void
(2) symphyseal diastasis or multiple fractures of the pubic rami
(3) radiolographic suggestion of a bladder neck injury.

The gold standard diagnostic tool in males is the retrograde urethrogram (RUG). Female injuries are often readily identified on CT, but a definitive diagnosis requires cystoscopy and vaginoscopy under general anesthesia (*53*, *54*, *60*).

Concomitant rectal injury occurs in approximately 15% of males under the age of 16 with urethral injuries. Digital rectal exam must be performed, and the presence of blood in the stool should prompt further evaluation with proctoscopy and possibly diverting colostomy (*10*).

MANAGEMENT

The management of urethral injuries is complex and should be undertaken by those with significant experience. The injuries in males are classified as either anterior or posterior. Posterior repairs can be further classified as early, delayed, or late repair. Universal principles of immediate treatment include the use of broad-spectrum antibiotics, assessment of the competence of the bladder neck, and aggressive urinary drainage (*10*).

(1) Immediate repair occurs within 48 h of the trauma. Primary realignment can occur by either by the gentle and easy passage of a urethral catheter or by endoscopic placement. This is especially effective for iatrogenic injuries, as most are partial urethral tears. Primary realignment may not necessarily decrease the incidence of stricture formation, but it results in a less severe injury and more simple reconstructive surgery (*62–65*). However, this may not be the case in complete urethral disruptions (*66*). Some early data suggested that primary realignment may have been associated with greater rates of impotence and incontinence, but most contemporary reviews would suggest that these complications are secondary to the injury, not the modality of repair (*62*, *63*, *67*).
(2) Delayed repairs are approached with the open placement of a suprapubic cystostomy tube and urethral repair in 2–14 days.
(3) Late repair refers to the patient who was initially managed with a suprapubic cystostomy tube, and definitive repair occurs later than 3 months after the initial injury. This allows the patient time to recover from the initial trauma

and inflammation of the tissue has resolved. The patient must be thoroughly assessed prior to surgery, as the urethral defect can be extensive. Definitive urethral anastomosis must be considered the gold standard in children, as the "cut to the light" procedures have been shown to have very poor long-term outcomes (*62*).

Before undertaking the delayed repair, simultaneous retrograde urethrogram and suprapubic cystogram are used to estimate the length of the defect and assess the competence of the bladder neck (*63*). Simple posterior repairs, up to 2 cm in length, can be repaired with an excision and anastomosis of the bulbar stricture, with a >95% success rate (*65*, *68*). Direct urethrotomy may be considered for post-operative short strictures, but should not be considered a long-term primary intervention. More extensive urethral defects may require pubectomy, an abdominoperoneal approach, or a trans-symphyseal route for the urethra (*68*, *69*). Defects >4 cm are often treated in a staged fashion, with excellent results attainable with buccal grafts.

Long-term morbidity can be significant with up to 70% of prostatic injuries associated with erectile dysfunction (*65*, *68*). Controversy exists regarding the etiology of impotence, and although most contemporary series report that this is due to the initial injury (*54*, *62*, *63*, *67*), some data has shown an association with the type of repair (*65*, *66*). Therefore, erectile deficiency needs to be thoroughly evaluated and documented before attempting any delayed repair (*70*).

GENITAL INJURIES

Traumatic genital injury is uncommon in pediatrics, and all healthcare providers must always be wary of abuse. In a recent review by Onen et al., 21% of their injuries were secondary to abuse (*71*). A thorough history has been shown to be the best determinant of accidental trauma versus abuse (*72*). However, physical exam can be difficult, and a prompt referral to an abuse specialist is highly recommended (*73*).

External female injuries include bruising and lacerations to the labia and vagina. Due to the etiology of these injuries, a high index of suspicion for associated urethral, pelvic, or rectal injuries must be maintained (*74*). Minor lacerations can usually be managed in the emergency department, with small absorbable suture for lacerations.

Larger lacerations, especially those involving the vagina, may bleed profusely. This mandates a thorough examination under anesthesia to completely assess and effectively repair. Vaginal bleeding is controlled with running absorbable sutures and post-operative vaginal packing (*74*).

Pediatric male external injuries primarily involve lacerations of the penis and scrotum, occurring secondary to a fall (*75*). Most of the lacerations are minor, but usually contaminated, so are best dealt with by irrigation and secondary healing. More extensive injuries will need surgical exploration

for more extensive debridement and primary closure, and may require cystoscopy to evaluate the proximal urethra. Extreme care must be taken with animal bites, with aggressive debridement, antibiotics, and vigilant post-operative monitoring (*76*).

The most common penile skin injury, however, is iatrogenic, secondary to a neonatal circumcision. Even an extensive penile degloving will heal very well with wet to dry dressings. If there has been a complete loss of the shaft skin, and it is available, the excised penile skin can be replaced as a full-thickness skin graft (*77*). Circumcision may also result in amputation of the glans, which requires immediate reattachment (*78*), or urethrocutaneous fistula (*79*), which can present immediately or in a delayed fashion.

A unique scenario in pediatrics is the "hair tourniquet." An errant hair becomes encircled around the shaft or glans, and can result in an insidious strangulation and ischemia (*76*). The hair can at times be difficult to see due to the associated edema. Early release routinely results in no long-term consequence (*10*). However, a late presentation can result in necrosis, urethrocutaneous fistula, or erosion through the neurovascular bundle and loss of sensation (*76*, *80*).

Scrotal Injury

With scrotal injuries, care must be taken to ensure the tunica vaginalis has not been violated, as this mandates irrigation and primary closure. Blunt trauma to the scrotum can also result in testicular rupture, mandating early surgical repair. Ultrasound and MRI are effective and making the diagnosis, but surgical exploration must be considered even if a definite violation of the tunica albuginea is not seen (*81*). A hematocele or intratesticular hematoma may herald a tunical rupture, 3with the potential of extruded seminiferous tubules, and therefore requiring intervention (*10*, *81*). A recent review of the American trauma registry revealed that no testicular injuries resulting in testicular loss were reported from team sports (*1*).

REFERENCES

1. Wan, J., Corvino, T. F., Greenfield, S. P., DiScala, C.: Kidney and testicle injuries in team and individual sports: data from the national pediatric trauma registry. J Urol, **170**: 1528, 2003
2. Buckley, J. C., McAninch, J. W.: Pediatric renal injuries: management guidelines from a 25-year experience. J Urol, **172**: 687, 2004
3. Master, V. A., McAninch, J. W., Santucci, R. A.: Genital self-mutilation and the Internet. J Urol, **164**: 1656, 2000
4. McAleer, I. M., Kaplan, G. W., LoSasso, B. E.: Congenital urinary tract anomalies in pediatric renal trauma patients. J Urol, **168**: 1808, 2002
5. Quinlan, D. M., Gearhart, J. P.: Blunt renal trauma in childhood. Features indicating severe injury. Br J Urol, **66**: 526, 1990
6. Morey, A. F., Bruce, J. E., McAninch, J. W.: Efficacy of radiographic imaging in pediatric blunt renal trauma. J Urol, **156**: 2014, 1996

7. Santucci, R. A., Wessells, H., Bartsch, G., Descotes, J., Heyns, C. F., McAninch, J. W. et al: Evaluation and management of renal injuries: consensus statement of the renal trauma subcommittee. BJU Int, **93**: 937, 2004
8. Chopra, P., St-Vil, D., Yazbeck, S.: Blunt renal trauma-blessing in disguise? J Pediatr Surg, **37**: 779, 2002
9. Heyns, C. F.: Renal trauma: indications for imaging and surgical exploration. BJU Int, **93**: 1165, 2004
10. Husmann, D.: Pediatric Genitourinary Trauma. In: Campbell-Walsh Urology, 8 ed. Edited by Walsh. Philadelphia: Saunders, vol. 4, 2007
11. Nguyen, M. M., Das, S.: Pediatric renal trauma. Urology, **59**: 762, 2002
12. Levy, J. B., Baskin, L. S., Ewalt, D. H., Zderic, S. A., Bellah, R., Snyder, H. M., 3rd et al: Nonoperative management of blunt pediatric major renal trauma. Urology, **42**: 418, 1993
13. Buckley, J. C., McAninch, J. W.: The diagnosis, management, and outcomes of pediatric renal injuries. Urol Clin North Am, **33**: 33, 2006
14. Wessel, L. M., Scholz, S., Jester, I., Arnold, R., Lorenz, C., Hosie, S. et al: Management of kidney injuries in children with blunt abdominal trauma. J Pediatr Surg, **35**: 1326, 2000
15. Bretan, P. N., Jr., McAninch, J. W., Federle, M. P., Jeffrey, R. B., Jr.: Computerized tomographic staging of renal trauma: 85 consecutive cases. J Urol, **136**: 561, 1986
16. Carpio, F., Morey, A. F.: Radiographic staging of renal injuries. World J Urol, **17**: 66, 1999
17. Santucci, R. A., McAninch, J. W., Safir, M., Mario, L. A., Service, S., Segal, M. R.: Validation of the American Association for the Surgery of Trauma organ injury severity scale for the kidney. J Trauma, **50**: 195, 2001
18. Smith, J. K., Kenney, P. J.: Imaging of renal trauma. Radiol Clin North Am, **41**: 1019, 2003
19. Moore, E. E., Shackford, S. R., Pachter, H. L., McAninch, J. W., Browner, B. D., Champion, H. R. et al: Organ injury scaling: spleen, liver, and kidney. J Trauma, **29**: 1664, 1989
20. McGahan, J. P., Richards, J. R., Jones, C. D., Gerscovich, E. O.: Use of ultrasonography in the patient with acute renal trauma. J Ultrasound Med, **18**: 207, 1999
21. Santucci, R. A., McAninch, J. M.: Grade IV renal injuries: evaluation, treatment, and outcome. World J Surg, **25**: 1565, 2001
22. Rogers, C. G., Knight, V., MacUra, K. J., Ziegfeld, S., Paidas, C. N., Mathews, R. I.: High-grade renal injuries in children--is conservative management possible? Urology, **64**: 574, 2004
23. Nance, M. L., Lutz, N., Carr, M. C., Canning, D. A., Stafford, P. W.: Blunt renal injuries in children can be managed nonoperatively: outcome in a consecutive series of patients. J Trauma, **57**: 474, 2004
24. Margenthaler, J. A., Weber, T. R., Keller, M. S.: Blunt renal trauma in children: experience with conservative management at a pediatric trauma center. J Trauma, **52**: 928, 2002
25. Smith, E. M., Elder, J. S., Spirnak, J. P.: Major blunt renal trauma in the pediatric population: is a nonoperative approach indicated? J Urol, **149**: 546, 1993
26. Al-Qudah, H. S., Santucci, R. A.: Complications of renal trauma. Urol Clin North Am, **33**: 41, 2006
27. Husmann, D. A., Gilling, P. J., Perry, M. O., Morris, J. S., Boone, T. B.: Major renal lacerations with a devitalized fragment following blunt abdominal trauma: a comparison between nonoperative (expectant) versus surgical management. J Urol, **150**: 1774, 1993
28. Wessells, H., Deirmenjian, J., McAninch, J. W.: Preservation of renal function after reconstruction for trauma: quantitative assessment with radionuclide scintigraphy. J Urol, **157**: 1583, 1997
29. Buckley, J. C., McAninch, J. W.: Selective management of isolated and nonisolated grade IV renal injuries. J Urol, **176**: 2498, 2006

30. Darcq, C., Guy, L., Garcier, J. M., Boyer, L., Boiteux, J. P: [Post-traumatic secondary arteriovenous fistulae of the kidney and their embolization. Report of 3 cases]. Prog Urol, **12**: 21, 2002
31. Uflacker, R., Paolini, R. M., Lima, S.: Management of traumatic hematuria by selective renal artery embolization. J Urol, **132**: 662, 1984
32. Benson, D. A., Stockinger, Z. T., McSwain, N. E., Jr.: Embolization of an acute renal arteriovenous fistula following a stab wound: case report and review of the literature. Am Surg, **71**: 62, 2005
33. Swana, H. S., Cohn, S. M., Burns, G. A., Egglin, T. K.: Renal artery pseudoaneurysm after blunt abdominal trauma: case report and literature review. J Trauma, **40**: 459, 1996
34. Pinto, I. T., Chimeno, P. C.: Treatment of a urinoma and a post-traumatic pseudoaneurysm using selective arterial embolization. Cardiovasc Intervent Radiol, **21**: 506, 1998
35. Matthews, L. A., Smith, E. M., Spirnak, J. P.: Nonoperative treatment of major blunt renal lacerations with urinary extravasation. J Urol, **157**: 2056, 1997
36. Moudouni, S. M., Patard, J. J., Manunta, A., Guiraud, P., Guille, F., Lobel, B.: A conservative approach to major blunt renal lacerations with urinary extravasation and devitalized renal segments. BJU Int, **87**: 290, 2001
37. Boone, T. B., Gilling, P. J., Husmann, D. A.: Ureteropelvic junction disruption following blunt abdominal trauma. J Urol, **150**: 33, 1993
38. Watts, R. A., Hoffbrand, B. I.: Hypertension following renal trauma. J Hum Hypertens, **1**: 65, 1987
39. Dobrowolski, Z., Kusionowicz, J., Drewniak, T., Habrat, W., Lipczynski, W., Jakubik, P. et al: Renal and ureteric trauma: diagnosis and management in Poland. BJU Int, **89**: 748, 2002
40. von Knorring, J., Fyhrquist, F., Ahonen, J.: Varying course of hypertension following renal trauma. J Urol, **126**: 798, 1981
41. Meyrier, A., Rainfray, M., Lacombe, M.: Delayed hypertension after blunt renal trauma. Am J Nephrol, **8**: 108, 1988
42. Lock, J. S., Carraway, R. P., Hudson, H. C., Jr., Laws, H. L.: Proper management of renal artery injury from blunt trauma. South Med J, **78**: 406, 1985
43. Stables, D. P., Fouche, R. F., de Villiers van Niekerk, J. P., Cremin, B. J., Holt, S. A., Peterson, N. E.: Traumatic renal artery occlusion: 21 cases. J Urol, **115**: 229, 1976
44. Santucci, R. A., McAninch, J. W.: What's my scale? Organ injury severity scaling in the new millennium. Curr Urol Rep, **2**: 335, 2001
45. Elliott, S. P., McAninch, J. W.: Ureteral injuries from external violence: the 25-year experience at San Francisco General Hospital. J Urol, **170**: 1213, 2003
46. Presti, J. C., Jr., Carroll, P. R., McAninch, J. W.: Ureteral and renal pelvic injuries from external trauma: diagnosis and management. J Trauma, **29**: 370, 1989
47. Kunkle, D. A., Kansas, B. T., Pathak, A., Goldberg, A. J., Mydlo, J. H.: Delayed diagnosis of traumatic ureteral injuries. J Urol, **176**: 2503, 2006
48. Toporoff, B., Sclafani, S., Scalea, T., Vieux, E., Atweh, N., Duncan, A. et al: Percutaneous antegrade ureteral stenting as an adjunct for treatment of complicated ureteral injuries. J Trauma, **32**: 534, 1992
49. Mendez, R., McGinty, D. M.: The management of delayed recognized ureteral injuries. J Urol, **119**: 192, 1978
50. Schuster, T. G., Russell, K. Y., Bloom, D. A., Koo, H. P., Faerber, G. J.: Ureteroscopy for the treatment of urolithiasis in children. J Urol, **167**: 1813, 2002
51. Wu, H. Y., Docimo, S. G.: Surgical management of children with urolithiasis. Urol Clin North Am, **31**: 589, 2004
52. Minevich, E., Defoor, W., Reddy, P., Nishinaka, K., Wacksman, J., Sheldon, C. et al: Ureteroscopy is safe and effective in prepubertal children. J Urol, **174**: 276, 2005
53. Boone, T. B., Wilson, W. T., Husmann, D. A.: Postpubertal genitourinary function following posterior urethral disruptions in children. J Urol, **148**: 1232, 1992

54. Husmann, D. A., Wilson, W. T., Boone, T. B., Allen, T. D.: Prostatomembranous urethral disruptions: management by suprapubic cystostomy and delayed urethroplasty. J Urol, **144**: 76, 1990
55. Metcalfe, P., Casale, A., Meldrum, K., Kaefer, M., Rink, R. C., Cain, M. P.: Spontaneous Perforation of the Augmented Bladder. J Urol, **175**: 1466, 2006
56. Pope, J., Albers, P., Rink, R., Casale, A., Cain, M., Keating, M.: Spontaneous Rupture of the Augmented Bladder: From Silence to Chaos. Presented at the European Society of Pediatric Urology, Istanbul, Turkey, 1999
57. Haas, C. A., Brown, S. L., Spirnak, J. P.: Limitations of routine spiral computerized tomography in the evaluation of bladder trauma. J Urol, **162**: 51, 1999
58. Kotkin, L., Koch, M. O.: Morbidity associated with nonoperative management of extraperitoneal bladder injuries. J Trauma, **38**: 895, 1995
59. Hemal, A. K., Dorairajan, L. N., Gupta, N. P.: Posttraumatic complete and partial loss of urethra with pelvic fracture in girls: an appraisal of management. J Urol, **163**: 282, 2000
60. Perry, M. O., Husmann, D. A.: Urethral injuries in female subjects following pelvic fractures. J Urol, **147**: 139, 1992
61. Routh, J. C., Husmann, D. A.: Long-term continence outcomes after immediate repair of pediatric bladder neck lacerations extending into the urethra. J Urol, **178**: 1816, 2007
62. Nerli, R. B., Koura, A. C., Ravish, I. R., Amarkhed, S. S., Prabha, V., Alur, S. B.: Posterior urethral injury in male children: long-term follow up. J Pediatr Urol, **4**: 154, 2008
63. Morey, A. F., Hernandez, J., McAninch, J. W.: Reconstructive surgery for trauma of the lower urinary tract. Urol Clin North Am, **26**: 49, 1999
64. Jepson, B. R., Boullier, J. A., Moore, R. G., Parra, R. O.: Traumatic posterior urethral injury and early primary endoscopic realignment: evaluation of long-term follow-up. Urology, **53**: 1205, 1999
65. Mouraviev, V. B., Coburn, M., Santucci, R. A.: The treatment of posterior urethral disruption associated with pelvic fractures: comparative experience of early realignment versus delayed urethroplasty. J Urol, **173**: 873, 2005
66. Podesta, M. L., Medel, R., Castera, R., Ruarte, A.: Immediate management of posterior urethral disruptions due to pelvic fracture: therapeutic alternatives. J Urol, **157**: 1444, 1997
67. Koch, M. O.: Primary realignment of prostatomembranous urethral disruptions. Semin Urol, **13**: 38, 1995
68. Cooperberg, M. R., McAninch, J. W., Alsikafi, N. F., Elliott, S. P.: Urethral reconstruction for traumatic posterior urethral disruption: outcomes of a 25-year experience. J Urol, **178**: 2006, 2007
69. Kizer, W. S., Armenakas, N. A., Brandes, S. B., Cavalcanti, A. G., Santucci, R. A., Morey, A. F.: Simplified reconstruction of posterior urethral disruption defects: limited role of supracrural rerouting. J Urol, **177**: 1378, 2007
70. Iselin, C. E., Webster, G. D.: The significance of the open bladder neck associated with pelvic fracture urethral distraction defects. J Urol, **162**: 347, 1999
71. Onen, A., Ozturk, H., Yayla, M., Basuguy, E., Gedik, S.: Genital trauma in children: classification and management. Urology, **65**: 986, 2005
72. Merritt, D. F.: Vulvar and genital trauma in pediatric and adolescent gynecology. Curr Opin Obstet Gynecol, **16**: 371, 2004
73. Makoroff, K. L., Brauley, J. L., Brandner, A. M., Myers, P. A., Shapiro, R. A.: Genital examinations for alleged sexual abuse of prepubertal girls: findings by pediatric emergency medicine physicians compared with child abuse trained physicians. Child Abuse Negl, **26**: 1235, 2002
74. Wessells, H., Long, L.: Penile and genital injuries. Urol Clin North Am, **33**: 117, 2006
75. Kadish, H. A., Schunk, J. E., Britton, H.: Pediatric male rectal and genital trauma: accidental and nonaccidental injuries. Pediatr Emerg Care, **14**: 95, 1998
76. El-Bahnasawy, M. S., El-Sherbiny, M. T.: Paediatric penile trauma. BJU Int, **90**: 92, 2002
77. Baskin, L. S., Canning, D. A., Snyder, H. M., Duckett, J. W.: Treating complications of circumcision. Pediatr Emerg Care, **12**: 62, 1996

78. Gluckman, G. R., Stoller, M. L., Jacobs, M. M., Kogan, B. A.: Newborn penile glans amputation during circumcision and successful reattachment. J Urol, **153**: 778, 1995
79. Baskin, L. S., Canning, D. A., Snyder, H. M., 3rd, Duckett, J. W., Jr.: Surgical repair of urethral circumcision injuries. J Urol, **158**: 2269, 1997
80. Radhakrishnan, J., Razzaq, A., Manickam, K.: Concealed penis. Pediatr Surg Int, **18**: 668, 2002
81. Mulhall, J. P., Gabram, S. G., Jacobs, L. M.: Emergency management of blunt testicular trauma. Acad Emerg Med, **2**: 639, 1995

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